

11INVENTOR SEARCH

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FILE CONTENT:1840 - 1 Apr 2007 VOL 146 ISS 15

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This file contains CAS Registry Numbers for easy and accurate substance identification.

L2 12 SEA FILE=CASREACT ABB=ON MICHEL D7/AU
 L3 72 SEA FILE=CASREACT ABB=ON 3-AMINO ALCOHOL#
 L4 2 SEA FILE=CASREACT ABB=ON L2 AND L3

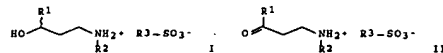
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L4 ANSWER 1 OF 2 CASREACT COPYRIGHT 2007 ACS ON STN
 ACCESSION NUMBER: 145:271387 CASREACT Full-text
 TITLE: Process for the preparation of enantiomerically pure 1-substituted-3-amino alcohols using methyl ketones, primary amines, formaldehydes and sulfonic acids
 INVENTOR(S): Brieden, Walter; Clausen, Martin; McGarrity, John; Mettler, Hanspeter; Michel, Dominique
 PATENT ASSIGNER(S): Lonza A.-G., Switz.
 SOURCE: PCT Int. Appl., 38pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 CLASSIFICATION: 23-15 (Aliphatic Compounds)
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006087166	A1	20060824	WO 2006-EP1334	20060214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				

1

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CP, CG, CI, CH, GA, GN, GO, GM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, WZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KZ, MD, RU, TJ, TM
 EP 1693371 A1 20060823 EP 2005-3657 20050221
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, ES, HU, PL, SK, BA, HR, IS, YU
 PRIORITY APPLN. INFO.: MARPAT 145:271387 20050221
 OTHER SOURCE(S):
 GRAPHIC IMAGE:



ABSTRACT:

Provided is a process for the preparation of N-monosubstituted β-aminoalcs. sulfonates of formula I. Comps. of formula I wherein R1 is (un)substituted C6-20 aryl or (un)substituted C4-12 heteroaryl; R2 is C1-4-alkyl or (un)substituted C6-20 aryl; R3 is selected from the group consisting of C1-18 alkyl, C6-20 cycloalkyl, C6-20 aryl and C7-20 aralkyl residues, and the process for preparing comps. of formula I are claimed. The process comprising the steps of a) reacting a Me ketone, a primary amine, formaldehyde and a sulfonic acid, at a pressure above 1.5 bar, optionally in a organic solvent, said organic solvent optionally containing water, to afford N-monosubstituted β-amino ketone sulfonates of formula II, wherein R1, R2 and R3 are as defined above, and b) asym. hydrogenating said sulfonates in the presence of a base and a catalyst, comprising a transition metal and a diphosphine ligand, in a polar solvent, optionally in the presence of water.

SUPPL. TERM: amino alc sulfonate asym prepn; methyl ketone amine formaldehyde sulfonic acid
 INDEX TERM: Ketones, preparation
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (amino; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
 INDEX TERM: Alcohols, preparation
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (chiral, amino; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
 INDEX TERM: Amines, preparation
 ROLE: SPN (Synthetic preparation); PREP (Preparation)

2

10/520362

(keto; preparation of enantiomerically pure sulfonate salts

substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
 INDEX TERM: Asymmetric synthesis and induction
 (preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

INDEX TERM: Hydrogenation
 Hydrogenation catalysts
 (stereoselective; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

INDEX TERM: 752258-19-8, (R,R,S,S)-TangPhos
 ROLE: CAT (Catalyst use); USES (Uses)
 ((R,R,S,S)-TangPhos, catalyst; preparation of

enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

INDEX TERM: 486429-94-1, (S)-C4-TunePhos
 ROLE: CAT (Catalyst use); USES (Uses)
 ((S)-C4-TunePhos, catalyst; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

INDEX TERM: 136735-95-0, (S,S)-Methyl-DuPHOS
 ROLE: CAT (Catalyst use); USES (Uses)
 ((S,S)-Me-DuPhos, catalyst; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

INDEX TERM: 7440-16-6, Rhodium, uses 7440-18-8, Ruthenium, uses 133545-16-1 133545-17-2, (S)-MeO-BiPhep 248244-33-9 528814-26-8
 ROLE: CAT (Catalyst use); USES (Uses)
 (catalyst; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

INDEX TERM: 863094-23-9P 863094-27-3P 906812-48-4P 906812-49-5P 906812-50-8P 906812-51-9P 906812-52-0P 906812-53-1P 906812-54-2P 906812-55-3P 906812-56-4P 906812-57-5P
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (product; preparation of enantiomerically pure sulfonate

salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)

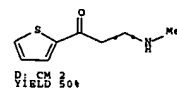
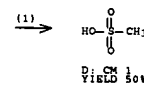
INDEX TERM: 50-00-0, Formaldehyde, reactions 88-15-3, 2-Acetylthiophene 104-15-4, p-Toluenesulfonic acid, reactions 110-88-3, 1,3,5-Trioxane, reactions 3144-16-9, (-)-Camphor-10-sulfonic acid 30525-89-4, Paraformaldehyde 116539-55-0 116539-57-2 206872-28-8, Methylammonium methanesulfonate 645411-16-1, 3-(Methylamino)-1-(2-thienyl)propan-1-one hydrochloride 863094-39-7 863094-46-6
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (starting material; preparation of enantiomerically pure

10/520362

sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
 REFERENCE COUNT: 6
 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Eli Lilly; EP 0457559 A 1991 CAPLUS
 (2) Fujisawa Pharmaceutical; JP 05070412 A 1993 CAPLUS
 (3) Lonza; WO 2004005239 A 2004 CAPLUS
 (4) Mannich, C; BERICHT DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT 1922, V55, P356
 (5) Sakuraba, S; CHEMICAL AND PHARMACEUTICAL BULLETIN 1995, V43(5), P748 CAPLUS
 (6) Wilkerson, W; US 4948813 A 1990 CAPLUS

RX(1) OF 6 A + B + C ==> D



RX(1) RCT A 206872-28-8, B 88-15-3, C 50-00-0

STAGE(1)
 SOL 64-17-5 EtOH
 CON 3 hours, 120 deg C, 4.5 bar

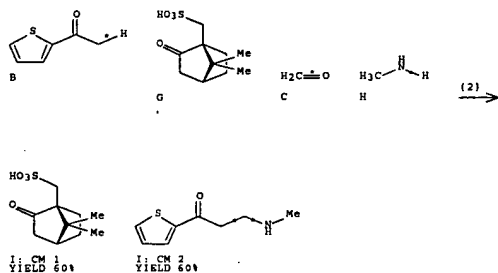
STAGE(2)
 SOL 64-17-5 EtOH, 141-78-6 AcOEt
 CON 30 minutes, 25 deg C

PRO D 906812-48-4
 NTE paraformaldehyde used, autoclave used, analogs prepd. similarly, thermal

3

4

RX(2) OF 6 B + G + C + H ==> I



RX(2) RCT B 88-15-3, G 3144-16-9, C 50-00-0, H 74-89-5

STAGE(1)

SOL 64-17-5 EtOH

CON 4 hours, 120 deg C, 4.5 - 4.8 bar

STAGE(2)

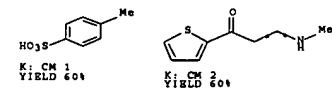
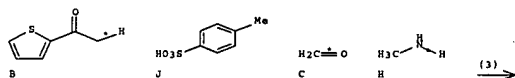
SOL 64-17-5 EtOH, 141-78-6 AcOEt

CON 30 minutes, 25 deg C

PRO I 906812-50-8

NTE paraformaldehyde used, autoclave used, thermal

RX(3) OF 6 B + J + C + H ==> K



RX(3) RCT B 88-15-3, J 104-15-4, C 50-00-0, H 74-89-5

STAGE(1)

SOL 64-17-5 EtOH

CON 4 hours, 120 deg C

STAGE(2)

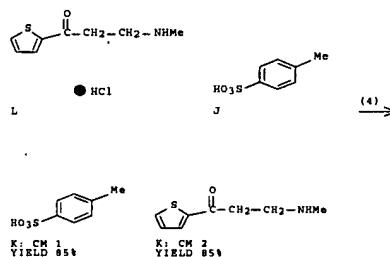
SOL 64-17-5 EtOH, 141-78-6 AcOEt

CON 30 minutes, 25 deg C

PRO K 863094-23-9

NTE paraformaldehyde used, autoclave used, thermal

RX(4) OF 6 L + J ==> K



RX(4) RCT L 645411-16-1

STAGE(1)

RGT M 1310-73-2 NaOH

SOL 7732-18-5 Water, 1634-04-4 t-BuOMe

CON SUBSTAGE(1) 15 minutes, 5 deg C

SUBSTAGE(2) 10 minutes, 5 deg C

STAGE(2)

RCT J 104-15-4

SOL 67-56-1 MeOH

CON SUBSTAGE(1) 15 minutes, 5 deg C

5

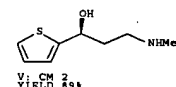
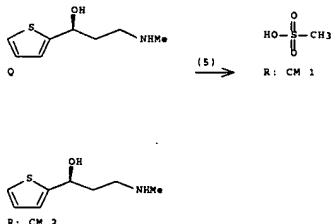
6

SUBSTAGE(2) 30 minutes, 25 deg C

PRO K 863094-23-9

NTE analogs prepd. similarly

RX(5) OF 6 Q ==> R



RX(6) RCT Q 116539-55-0, G 3144-16-9

STAGE(1)

SOL 64-17-5 EtOH, 141-78-6 AcOEt

CON SUBSTAGE(1) 40 minutes, 30 deg C

SUBSTAGE(2) 15 minutes, 50 deg C

STAGE(2)

SOL 141-78-6 AcOEt

CON SUBSTAGE(1) 15 minutes, reflux

SUBSTAGE(2) 30 minutes, reflux -> 25 deg C

PRO V 906812-57-5

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RX(5) RCT Q 116539-55-0

STAGE(1)

RGT S 584-08-7 K2CO3

CAT 528814-26-8 1,1'-Bi-1H-isophosphindole, 2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-, (1R,1'R,2S,2'S)-

SOL 7732-18-5 Water, 67-56-1 MeOH

CON room temperature

STAGE(2)

RGT T 1333-74-0 H2

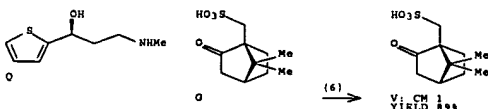
CON 21 hours, 40 deg C, 10 bar

PRO R 906812-56-4

NTE analogs prepd. similarly, autoclave used, high pressure, stereoselective

L4 ANSWER 2 OF 2 CASREACT COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 143:248273 CASREACT Full-text
 TITLE: Preparation of enantiomerically pure 1-substituted-3-amino alcohols
 INVENTOR(S): Michel, Dominique
 PATENT ASSIGNEE(S): Lonza A.-G., Switz.
 SOURCE: Eur. Pat. Appl., 14 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 INT. PATENT CLASSIF.:
 MAIN: C07D333-20
 SECONDARY: C07D333-22; C07C213-00; C07B053-00
 CLASSIFICATION: 27-8 (Heterocyclic Compounds (One Hetero Atom))
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

RX(6) OF 6 Q + G ==> V



PATENT NO. KIND DATE APPLICATION NO. DATE
 EP 1566383 A1 20050824 EP 2004-3809 20040219
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, ER, HU, SK
 AU 2005215906 A1 20050901 AU 2005-215906 20050221
 CA 2556891 A1 20050901 CA 2005-2556891 20050221
 WO 2005080370 A1 20050901 WO 2005-EP1781 20050221
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MA, MD, ME, MG, MH, MI, MN, MO, MP, MQ, MR, MU, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

7

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

EP 1720852 A1 20061115 EP 2005-715425 20050221

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

CN 1922168 A 20070228 CN 2005-8005452 20050221

NO 200604017 A 20060915 NO 2006-4017 20060906

PRIORITY APPLN. INFO.: EP 2004-3809 20040219

WO 2004-10043 20040428

WO 2005-EP1781 20050221

OTHER SOURCE(S): MARPAT 143:248273

ABSTRACT:

Provided is a process for the preparation of enantiomerically pure 1-substituted-3-amino alcs. (R)- or (S)-HOCH(R1)CH2CH2NHR2 (R1 = 2-thienyl, 2-furanyl, Ph, substituted 2-thienyl, substituted 2-furanyl, substituted Ph; R2 = Cl-C4-alkyl, Ph, substituted Cl-C4-alkyl, substituted Ph), particularly (S)-(-)- and (R)-(+)-3-N-methylamino-1-(2-thienyl)-1-propanol, by asym. hydrogenating salts of R1COCH2CH2NHR2 using Rh and an asym. ligand.

SUPPL. TERM: alc amino asym prep rhodium chiral ligand hydrogenation; hydrogenation asym amino ketone amino alc prep

INDEX TERM: Alcohols, preparation

ROLE: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (amino; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Ketones, reactions

ROLE: RCT (Reactant); RACT (Reactant or reagent)

INDEX TERM: (amino; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Asymmetric synthesis and induction

INDEX TERM: Amines, reactions

ROLE: RCT (Reactant); RACT (Reactant or reagent)

INDEX TERM: (keto; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Hydrogenation

INDEX TERM: (stereoselective; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 116539-55-OP, (S)-(-)-3-(N-Methylamino)-1-(2-thienyl)-1-propanol 116539-57-2P 863094-39-7P 863094-46-6P

ROLE: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (amino; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 88-15-3, 2-Acetylthiophene

ROLE: RCT (Reactant); RACT (Reactant or reagent)

INDEX TERM: (asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 569687-76-9P 645411-16-1P, 3-(N-Methylamino)-1-(2-thienyl)-1-propanone hydrochloride 863094-06-8P 863094-15-9P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: (asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 133545-16-1 133545-17-2 136735-95-0 248244-33-9

486429-94-1 752258-19-8

ROLE: RGT (Reagent); RACT (Reactant or reagent)

INDEX TERM: (asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

116539-56-1P 863094-12-6P 863094-19-3P 863094-27-3P 863094-35-3P

ROLE: SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

REFERENCE COUNT: 10

REFERENCE(S): (1) THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD.

(1) Becker, H; WISSENSCHAFTLICHE ZEITSCHRIFT DER TECHNISCHEN HOCHSCHULE FUR CHEMIE 1969, VII(1), P38

(2) Fujisawa Pharm Co Ltd; JP 05070412 A 1993 CAPLUS

(3) Jua, A; WO 03070720 A 2003 CAPLUS

(4) Lilly Co Eli; EP 0457559 A 1991 CAPLUS

(5) Lonza Ag; WO 2004005239 A 2004 CAPLUS

(6) Lonza Ag; WO 2004005307 A 2004 CAPLUS

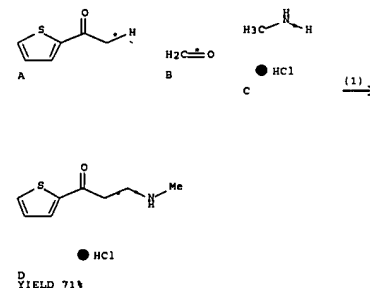
(7) Michael, R; US 6008412 A 1999 CAPLUS

(8) Robertson, D; JOURNAL OF MEDICINAL CHEMISTRY 1988, P1412 CAPLUS

(9) Sakai, K; TETRAHEDRON: ASYMMETRY 2003, VI4(12), P1631 CAPLUS

(10) Sakuraba, S; CHEMICAL AND PHARMACEUTICAL BULLETIN 1995, V43(5), P748 CAPLUS

RX(1) OF 31 A + B + C ==> D...



RX(1) RCT A 88-15-3, B 50-00-0, C 593-51-1

PRO D 645411-16-1

SOL 64-17-5 EtOH

CON SUBSTAGE(1) 9 hours, 120 - 130 deg C

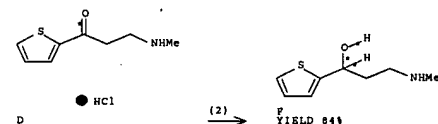
SUBSTAGE(2) 130 deg C -> 20 deg C

NTE paraformaldehyde used, autoclave used

9

10

RX(2) OF 31 ...D ==> F



RX(2) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH

SOL 7732-18-5 Water, 64-17-5 EtOH

CON 5 minutes, 4 deg C

STAGE(2)

RGT H 16940-66-2 NaBH4

CON SUBSTAGE(1) 30 minutes, 4 deg C

SUBSTAGE(2) 4 hours, 4 deg C

STAGE(3)

RGT I 67-64-1 Me2CO

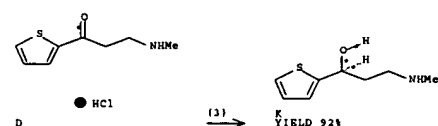
CON SUBSTAGE(1) 5 minutes

SUBSTAGE(2) 10 minutes

PRO F 116539-56-1

NTE incremental addition of sodium borohydride in second stage

RX(3) OF 31 ...D ==> K



RX(3) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH

SOL 67-56-1 MeOH

CON room temperature

STAGE(2)

SOL 67-56-1 MeOH

CON SUBSTAGE(1) room temperature

SUBSTAGE(2) room temperature -> 50 deg C

STAGE(3)

RGT L 1333-74-0 H2

CON SUBSTAGE(1) 50 deg C, 30 bar

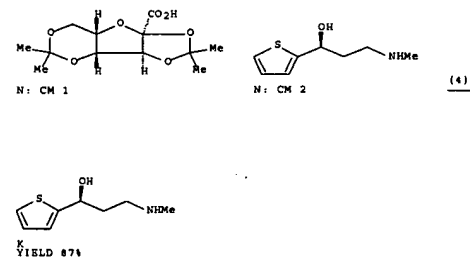
SUBSTAGE(2) 5 hours, 50 deg C

SUBSTAGE(3) 50 deg C -> room temperature

PRO K 116539-55-0

NTE [Rh((S,S)-Me-Duphos)]BF4 used as catalyst stage 2, stereoselective, autoclave used, high pressure in last stage, ee = 97%, optimized on catalyst

RX(4) OF 31 ...N ==> K



RX(4) RCT N 569687-76-9

RGT G 1310-73-2 NaOH

PRO K 116539-55-0

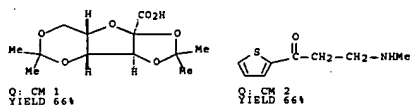
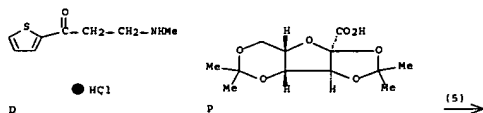
SOL 7732-18-5 Water, 75-09-2 CH2Cl2

CON SUBSTAGE(1) room temperature

SUBSTAGE(2) 15 minutes, room temperature

NTE incremental addition of reactant

RX(5) OF 31 ...D + P ==> Q...



RX(5) RCT D 645411-16-1

STAGE(1)

RGT Q 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 0 deg C
 SUBSTAGE(2) 15 minutes, 0 deg C
 SUBSTAGE(3) 10 minutes, 0 deg C

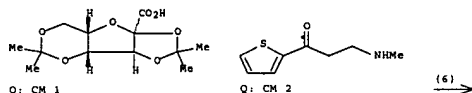
STAGE(2)

RCT P 18467-77-1
 SOL 1634-04-4 t-BuOMe
 CON room temperature

PRO Q 863094-06-8

NTE scalable

RX(6) OF 31 ...Q ==> N...



13

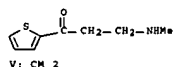
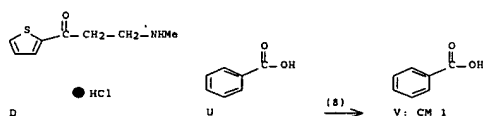
SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)

RCT S 526-98-7
 SOL 1634-04-4 t-BuOMe
 CON 15 minutes, <10 deg C

PRO T 863094-12-6

RX(8) OF 31 ...D + U ==> V...



RX(8) RCT D 645411-16-1

STAGE(1)

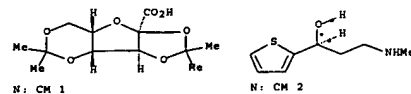
RGT Q 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)

RCT U 65-85-0
 SOL 1634-04-4 t-BuOMe
 CON 15 minutes, <10 deg C

PRO V 863094-15-9

RX(9) OF 31 ...V ==> W



RX(6) RCT Q 863094-06-8

STAGE(1)

SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature
 SUBSTAGE(3) room temperature -> 50 deg C

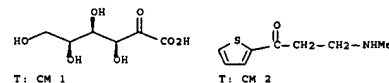
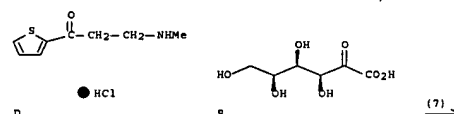
STAGE(2)

RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C -> room temperature

PRO N 569687-76-9

NTE [Rh((R,R,S,S)-tangphos)(norbornadiene)]BF4 used as catalyst
 stage 1, stereoselective, high pressure in last stage, autoclave
 used, ee = 95%, conversion is 100%

RX(7) OF 31 ...D + S ==> T

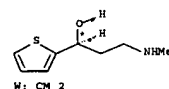
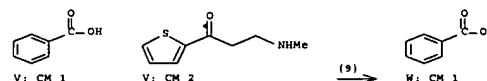


RX(7) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH

14



RX(9) RCT V 863094-15-9

STAGE(1)

CAT 205064-10-4 Rhodium(1+), [(1,2,5,6-η)-1,5-cyclooctadiene][(2S,2'S,5S,5'S)-(1,1'-(1,2-phenylene)bis(2,5-dimethylphospholane-xP))]-, tetrafluoroborate(1-)
 SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature -> 50 deg C

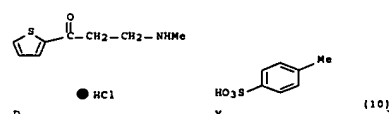
STAGE(2)

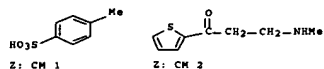
RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C -> room temperature

PRO W 863094-19-3

NTE stereoselective, high pressure in last stage, autoclave used, ee = 96.7%, conversion is 99%

RX(10) OF 31 ...D + Y ==> Z...





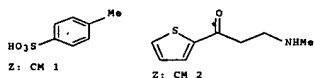
RX(10) RCT D 645411-16-1

STAGE(1)
 RGT G 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

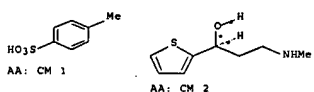
STAGE(2)
 RCT Y 104-15-4
 SOL 1634-04-4 t-BuOMe
 CON 15 minutes, <10 deg C

PRO Z 863094-23-9

RX(11) OF 31 ...Z ==> AA



(11)



RX(11) RCT Z 863094-23-9

STAGE(1)
 CAT 205064-10-4 Rhodium(1+), [(1,2,5,6-η)-1,5-cyclooctadiene] [(2S,2'S,5S,5'S)-1,1'-(1,2-phenylene)bis[2,5-dimethylphospholane-κP]]-, tetrafluoroborate(1-)
 SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature -> 50 deg C

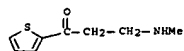
17

STAGE(2)
 RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C -> room temperature

PRO AA 863094-27-3

NTE stereoselective, high pressure in last stage, autoclave used, ee = 90%, conversion is 5%

RX(12) OF 31 ...D + AB ==> AC...



● HCl

HO2C-(CH2)10-Me

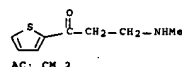
(12)

D

AB

HO2C-(CH2)10-Me

AC: CM 1



RX(12) RCT D 645411-16-1

STAGE(1)
 RGT G 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)
 RCT AB 143-07-7
 SOL 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) 15 minutes, <10 deg C
 SUBSTAGE(2) 1 hour

PRO AC 863094-31-9

RX(13) OF 31 ...AC ==> AD

REACTION SEARCH

FILE 'CASREACT' ENTERED AT 15:29:11 ON 03 APR 2007
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FILE CONTENT:1840 - 1 Apr 2007 VOL 146 ISS 15

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 * CASREACT now has more than 12 million reactions *

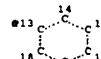
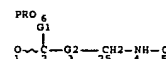
Some CASREACT records are derived from the ZIC/VINITI database (1974-1999) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

>> d stat que 127

L15

STR



Ak #19

Ak-O-Ak
#20 21 22Ak-X
#23 24

VAR G1=19/20/23/13

REP G2=(0-2) CH2

NODE ATTRIBUTES:

NSPEC IS RC AT 5

NSPEC IS RC AT 11

CONNECT IS E1 RC AT 1

CONNECT IS E1 RC AT 9

CONNECT IS E1 RC AT 19

CONNECT IS E1 RC AT 22

DEFAULT MLEVEL IS ATOM

GGCAT IS LOC SAT AT 9

DEFAULT ELEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 25

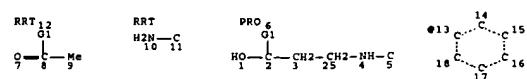
19

20

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM ROL NOD SYM ROL
 5 C PRO 11 C RRT
 11 C RRT 5 C PRO
 L19 150 SEA FILE=CASREACT SSS FUL L15 (722 REACTIONS)
 L24 STR



AK #19 AK-O-AK
 #20 21 22 #23 24

VAR G1-19/20/23/13

NODE ATTRIBUTES:

NSPEC IS RC AT 5
 NSPEC IS RC AT 11
 CONNECT IS E1 RC AT 19
 CONNECT IS E1 RC AT 22
 DEFAULT MLEVEL IS ATOM
 MLEVEL IS CLASS AT 1
 DEFAULT ELEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM ROL NOD SYM ROL
 5 C PRO 11 C RRT
 11 C RRT 5 C PRO
 L27 8 SEA FILE=CASREACT SUB=L19 SSS FUL L24 (26 REACTIONS)

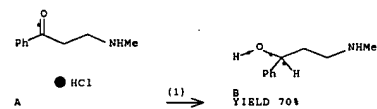
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L27 ANSWER 1 OF 8 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 146:62451 CASREACT Full-text
 TITLE: Method for synthesis of 3-methylamino-1-phenylpropanol
 INVENTOR(S): Yang, Guoming; Huang, Shengjian; Chen, Xia
 PATENT ASSIGNEE(S): Shangyu Zhongke Baiyun Fine Chemical Research Center Co., Ltd., Peop. Rep. China
 SOURCE: Faming Zhuanli Shengqing Gongkai Shuomingshu, 10 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: Chinese

21



RX(1) RCT A 2538-50-3

STAGE(1)

RGT C 1333-74-0 H2
 CAT 7440-02-0 Ni
 SOL 7732-18-5 Water
 CON 70 deg C, 1 MPa

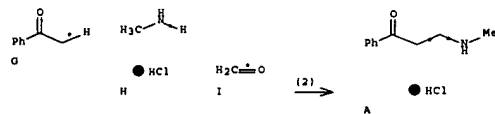
STAGE(2)

RGT D 1310-73-2 NaOH
 SOL 7732-18-5 Water
 CON pH 11

PRO B 42142-52-9

NTE Raney Nickel used, optimization study, optimized on pH, stoichiometry, pressure, temperature

RX(2) OF 3 G + H + I ==> A...



RX(2) RCT G 98-86-2, H 593-51-1, I 50-00-0

PRO A 2538-50-3

SOL 64-17-5 EtOH

CON 90 deg C

NTE Mannich reaction, optimization study, optimized on stoichiometry, temperature, paraformaldehyde used

L27 ANSWER 2 OF 8 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 142:481782 CASREACT Full-text

TITLE: Practical synthesis of enantiopure γ -amino alcohols by rhodium-catalyzed asymmetric hydrogenation of β -secondary-amino ketones
 AUTHOR(S): Liu, Duan; Ge, Wenzhong; Wang, Chunjiang; Zhang, Xumu
 CORPORATE SOURCE: Department of Chemistry, The Pennsylvania State University, University Park, PA, 16802, USA

22

CLASSIFICATION: 25-7 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1865226	A	20061122	CN 2006-10052037	20060619
			CN 2006-10052037	20060619

PRIORITY APPLN. INFO.:

ABSTRACT:
 The title method comprises the steps: (1) dissolving hypnone, paraformaldehyde and monomethylamine hydrochloride in alc. in an autoclave kettle, heating to 60-100°, concentrating the solution after the reaction, cooling and crystallizing to obtain 3-methylamino-1-phenylpropanol hydrochloride; (2) reducing in the solvent with the catalyst to obtain 3-methylamino-1-phenylpropanol hydrochloride solution; (3) adjusting pH to 9-14 with a base solution, extracting, recycling the solvent and recrystg. with cyclohexane to obtain 3-methylamino-1-phenylpropanol. In step 2, the catalyst is Raney-Ni, the hydrogen pressure is 0.3-1.5 MPa, temperature 25-80°. The method has the advantages of high product yield and quality, low cost and less wastes.

SUPPL. TERM: methylaminophenylpropanol prep hypnone paraformaldehyde

INDEX TERM: monomethylamine hydrochloride catalytic hydrogenation Hydrogenation

INDEX TERM: (synthesis of methylaminophenylpropanol from hypnone, paraformaldehyde and monomethylamine hydrochloride via catalytic hydrogenation)

INDEX TERM: 7440-02-0, Raney-Nickel, uses

ROLE: CAT (Catalyst use); USES (Uses)
 (catalytic; synthesis of methylaminophenylpropanol from hypnone, paraformaldehyde and monomethylamine hydrochloride via catalytic hydrogenation)

INDEX TERM: 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 110-82-7, Cyclohexane, uses

ROLE: NUU (Other use, unclassified); USES (Uses)
 (synthesis of methylaminophenylpropanol from hypnone, paraformaldehyde and monomethylamine hydrochloride via catalytic hydrogenation)

INDEX TERM: 98-86-2, Hypnone, reactions 593-51-1, Methylamine hydrochloride 30525-89-4, Paraformaldehyde

ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (synthesis of methylaminophenylpropanol from hypnone, paraformaldehyde and monomethylamine hydrochloride via catalytic hydrogenation)

INDEX TERM: 2538-50-3P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of methylaminophenylpropanol from hypnone, paraformaldehyde and monomethylamine hydrochloride via catalytic hydrogenation)

INDEX TERM: 42142-52-9P, 3-Methylamino-1-phenylpropanol

ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (synthesis of methylaminophenylpropanol from hypnone, paraformaldehyde and monomethylamine hydrochloride via catalytic hydrogenation)

RX(1) OF 3 ...A ==> B

22

SOURCE: Angewandte Chemie, International Edition (2005), 44(11), 1687-1689
 CODEN: ACIEF5; ISSN: 1433-7851
 PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 CLASSIFICATION: 25-7 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 27

ABSTRACT:
 Several β -secondary amino ketone hydrochlorides were hydrogenated with remarkably high enantioselectivities by using a rhodium complex containing P-chiral bisphospholane. These results establish a short and practical means for the synthesis of enantiopure N-monosubstituted γ -amino alcs., which are key intermediates in the synthesis of important antidepressants. For example, the bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation of 3-(methylamino)-1-phenyl-1-propanone hydrochloride gave (aS)- α -(2-[(methyl)amino]ethyl)benzenemethanol, which is a synthetic precursor for (yS)-N-methyl- γ -(4-(trifluoromethyl)phenoxy)benzenepropanamine [i.e., (S)-fluoxetine]. The synthesis of (aS)-[1-[(methyl)amino]ethyl]thiophenemethanol, a key synthetic intermediate for (S)-duloxetine, was also reported.

SUPPL. TERM: enantiopure aminoalkanol rhodium asym hydrogenation secondary amino ketone; fluoxetine duloxetine asym synthesis hydrogenation amino ketone hydrochloride

INDEX TERM: Alcohols, preparation

ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (aralkyl, α -(aminoalkyl), chiral; preparation of [(methyl)amino]ethylarenemethanol by tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)[(methyl)amino]propanone hydrochloride as synthetic intermediate)

INDEX TERM: Alcohols, preparation

ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (benzyl, α -(aminoalkyl), chiral; preparation of [(methyl)amino]ethylarenemethanol deriva. by 1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)[(methyl)amino]propanone hydrochloride as synthetic intermediate)

INDEX TERM: Asymmetric synthesis and induction
 (preparation of chiral [(methyl)amino]ethylarenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)[(methyl)amino]propanone hydrochloride as synthetic intermediate)

INDEX TERM: Asymmetric synthesis and induction catalysts
 (preparation of chiral [(methyl)amino]ethylarenemethanol by tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)[(methyl)amino]propanone hydrochloride as synthetic intermediate)

INDEX TERM: Hydrogenation
 Hydrogenation catalysts
 (stereoselective; preparation of chiral [(methyl)amino]ethylarenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-

24

INDEX TERM: isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: Ketones, preparation

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: ((m-amino, hydrochlorides; preparation of [(methyl)amino]ethyl)arenemethanol by tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using m-(alkyl)amino ketone hydrochlorides as synthetic intermediates)

INDEX TERM: 116539-59-4P, (S)-Duloxetine

INDEX TERM: ROLE: SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (preparation of (S)-duloxetine using (aS)-[(methyl)amino]ethyl)thiophenemethanol as synthetic intermediate)

INDEX TERM: 100568-02-3P, (S)-Fluoxetine

INDEX TERM: ROLE: SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (preparation of (S)-fluoxetine using (aS)-[(methyl)amino]ethyl)benzenemethanol as synthetic intermediate)

INDEX TERM: 114133-37-8P

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: (preparation of (aS)-[(methyl)amino]ethyl)benzenemethanol by bis(di(methyl)ethyl)tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation of [(methyl)amino] (phenyl)-1-propanone hydrochloride)

INDEX TERM: 116539-55-0P

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: (preparation of (aS)-[(methyl)amino]ethyl)thiophenemethanol by bis(di(methyl)ethyl)tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation of [(methyl)amino] (thienyl)-1-propanone hydrochloride)

INDEX TERM: 88-15-3, 1-(2-Thienyl)ethanone 93-08-3, 1-(2-Naphthyl)ethanone 98-86-2, 1-(Phenyl)ethanone, reactions 99-90-1, 1-(4-Bromophenyl)ethanone 100-06-1, 1-(4-Methoxyphenyl)ethanone 577-16-2, 1-(2-Methylphenyl)ethanone 579-74-8, 1-(2-Methoxyphenyl)ethanone 593-51-1 2142-63-4, 1-(3-Bromophenyl)ethanone 30525-89-4, Paraformaldehyde

INDEX TERM: ROLE: RCT (Reactant); RACT (Reactant or reagent)

INDEX TERM: (preparation of [(methyl)amino] (aryl)-1-propanone hydrochloride using paraformaldehyde, (methyl)amine hydrochloride and (aryl)ethanone as starting materials)

INDEX TERM: 3287-99-8

INDEX TERM: ROLE: RCT (Reactant); RACT (Reactant or reagent)

INDEX TERM: (preparation of [(phenyl)methyl]amino] (aryl)-1-propanone hydrochloride using paraformaldehyde, (benzyl)amine hydrochloride and (aryl)ethanone as starting materials)

INDEX TERM: 35274-92-1P

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: (preparation of chiral [(benzyl)amino]ethyl)arenemethanol by bis(di(methyl)ethyl)tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective

25

hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: 2538-50-3P 24206-62-0P 645411-16-1P 645411-21-8P 851878-34-7P 851878-36-9P 851878-38-1P 851878-40-5P

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: (preparation of chiral [(methyl)amino]ethyl)arenemethanol by bis(di(methyl)ethyl)tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: 116539-57-2P 851878-71-2P 851878-74-5P 851878-76-7P 851878-78-9P 851878-80-3P 851878-82-5P 851878-86-9P

INDEX TERM: ROLE: SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (preparation of chiral [(methyl)amino]ethyl)arenemethanol by bis(di(methyl)ethyl)tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: 850780-91-5 851936-69-1

INDEX TERM: ROLE: CAT (Catalyst use); USES (Uses)

INDEX TERM: (preparation of chiral γ -amino alc. derivs. by stereoselective hydrogenation of β -secondary amino ketone derivs. using chiral bis(di(methyl)ethyl)tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium as catalyst)

INDEX TERM: 34597-73-4P

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

INDEX TERM: (preparation of γ -amino alc. derivative by hydrogenation of [(benzyl)amino] (aryl)-1-propanone hydrochloride derivative)

INDEX TERM: 851878-69-8P

INDEX TERM: ROLE: SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (preparation of γ -amino alc. derivative by hydrogenation of [(benzyl)amino] (aryl)-1-propanone hydrochloride derivative)

INDEX TERM: 42142-52-9P 69261-99-3P 851878-46-1P 851878-52-9P 851878-56-3P 851878-60-9P

INDEX TERM: ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

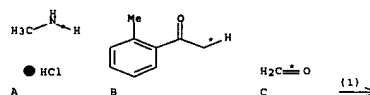
INDEX TERM: (preparation of γ -amino alc. derivative by hydrogenation of [(methyl)amino] (aryl)-1-propanone hydrochloride derivative)

INDEX TERM: 116539-56-1P 851878-48-3P 851878-50-7P 851878-54-1P 851878-58-5P 851878-62-1P 851878-65-4P 851878-67-6P

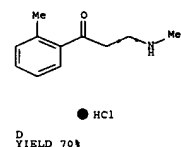
INDEX TERM: ROLE: SPN (Synthetic preparation); PREP (Preparation)

INDEX TERM: (preparation of γ -amino alc. derivative by hydrogenation of [(methyl)amino] (aryl)-1-propanone hydrochloride derivative)

RX(1) OF 74 A + B + C ==> D...



26



RX(1) RCT A 593-51-1, B 577-16-2, C 50-00-0

STAGE(1)

RGT 5 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

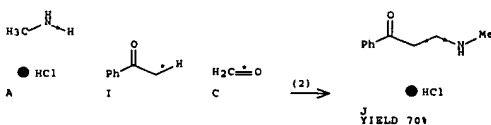
SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO D 851878-34-7

NTE paraformaldehyde used

RX(2) OF 74 A + I + C ==> J...



RX(2) RCT A 593-51-1, I 98-86-2, C 50-00-0

STAGE(1)

RGT 5 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

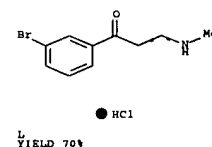
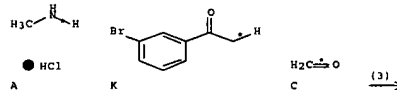
SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO J 2538-50-3

NTE paraformaldehyde used

RX(3) OF 74 A + K + C ==> L...



RX(3) RCT A 593-51-1, K 2142-63-4, C 50-00-0

STAGE(1)

RGT 5 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

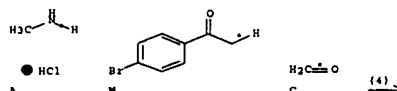
SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO L 851878-36-9

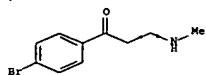
NTE paraformaldehyde used

RX(4) OF 74 A + M + C ==> N...



27

28



● HCl

N
YIELD 70%

RX(4) RCT A 593-51-1, M 99-90-1, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO N 851878-38-1

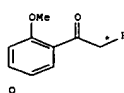
NTE paraformaldehyde used

RX(5) OF 74' A + O + C ==> P...



● HCl

A

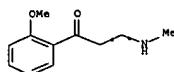


O



C

(5) →



● HCl

P
YIELD 70%

RX(5) RCT A 593-51-1, O 579-74-8, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

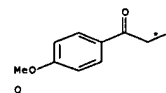
PRO P 851878-40-5

NTE paraformaldehyde used

RX(6) OF 74 A + Q + C ==> R...



A

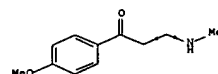


Q



C

(6) →



● HCl

R
YIELD 70%

RX(6) RCT A 593-51-1, Q 100-06-1, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO R 24206-62-0

NTE paraformaldehyde used

29

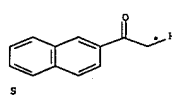
30

RX(7) OF 74 A + S + C ==> T...



● HCl

A

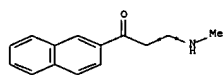


S



C

(7) →



● HCl

T
YIELD 70%

RX(7) RCT A 593-51-1, S 93-08-3, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO T 645411-21-8

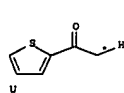
NTE paraformaldehyde used

RX(8) OF 74 A + U + C ==> V...



● HCl

A

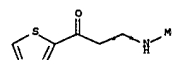


U



C

(8) →



● HCl

V
YIELD 70%

RX(8) RCT A 593-51-1, U 88-15-3, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO V 645411-16-1

NTE paraformaldehyde used

RX(9) OF 74 I + W + C ==> X...



I



W

● HCl



C

(9) →



● HCl

X
YIELD 70%

RX(9) RCT I 98-86-2, W 3287-99-8, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

31

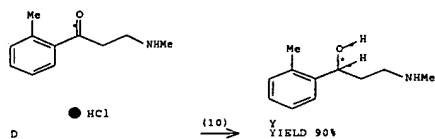
32

SOL 7732-18-5 Water, 64-17-5 EtOH
CON SUBSTAGE(1) 9 - 20 hours, 110 deg C
SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)
SOL 141-78-6 AcOBt
CON 4 hours, room temperature

PRO X 35274-92-1
NTE paraformaldehyde used

RX(10) OF 74 ...D ==> Y...



RX(10) RCT D 851878-34-7

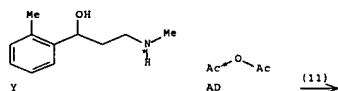
STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

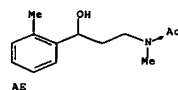
STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO Y 851878-46-1

RX(11) OF 74 ...Y + AD ==> AE

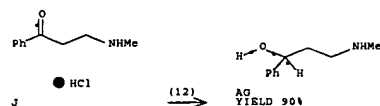


33



RX(11) RCT Y 851878-46-1, AD 108-24-7
PRO AE 851878-48-3
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(12) OF 74 ...J ==> AG...



RX(12) RCT J 2538-50-3

STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

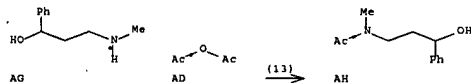
STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO AG 42142-52-9

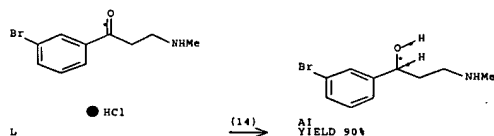
RX(13) OF 74 ...AG + AD ==> AH

34



RX(13) RCT AG 42142-52-9, AD 108-24-7
PRO AH 851878-50-7
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(14) OF 74 ...L ==> AI...



RX(14) RCT L 851878-36-9

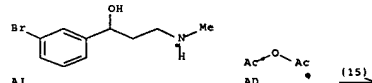
STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

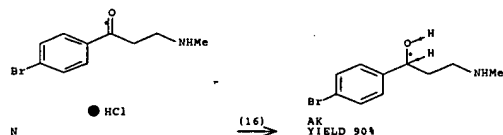
PRO AI 851878-52-9

RX(15) OF 74 ...AI + AD ==> AJ



RX(15) RCT AI 851878-52-9, AD 108-24-7
PRO AJ 851878-54-1
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(16) OF 74 ...N ==> AK...



RX(16) RCT N 851878-38-1

STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

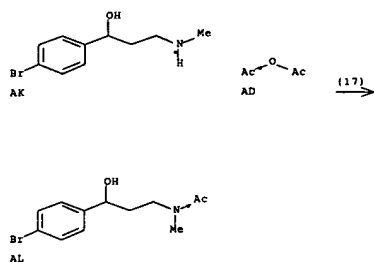
STAGE(3)
RGT AB 1310-73-2 NaOH

35

36

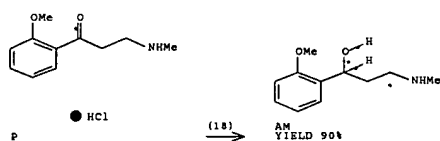
SOL 7732-18-5 Water
CON room temperature, basify
PRO AK 851878-56-3

RX(17) OF 74 ...AK + AD ==> AL



RX(17) RCT AK 851878-56-3, AD 108-24-7
PRO AL 851878-58-5
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

RX(18) OF 74 ...P ==> AM...



RX(18) RCT P 851878-40-5

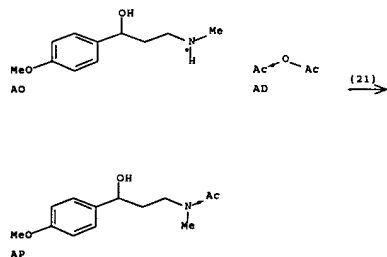
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

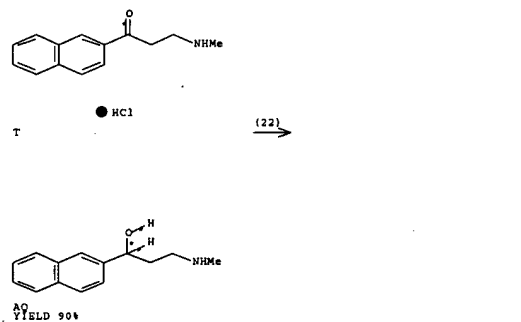
PRO AO 693261-99-3

RX(21) OF 74 ...AO + AD ==> AP



RX(21) RCT AO 693261-99-3, AD 108-24-7
PRO AP 851878-65-4
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

RX(22) OF 74 ...T ==> AQ



RX(22) RCT T 645411-21-8

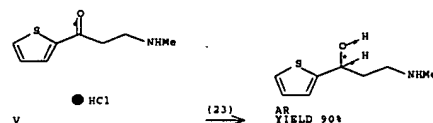
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO AQ 851878-67-6

RX(23) OF 74 ...V ==> AR



RX(20) RCT R 24206-62-0

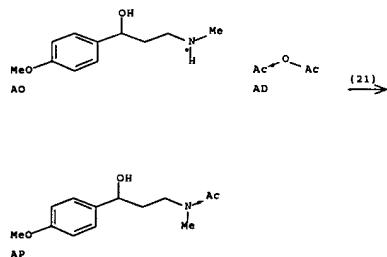
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

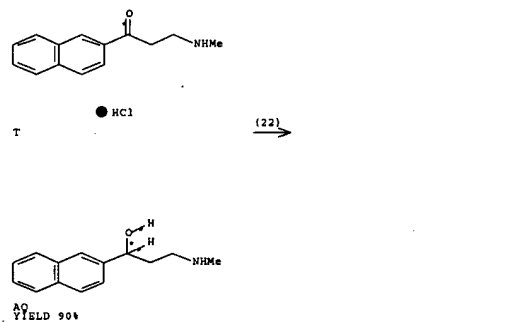
PRO AO 693261-99-3

RX(21) OF 74 ...AO + AD ==> AP



RX(21) RCT AO 693261-99-3, AD 108-24-7
PRO AP 851878-65-4
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

RX(22) OF 74 ...T ==> AQ



RX(22) RCT T 645411-21-8

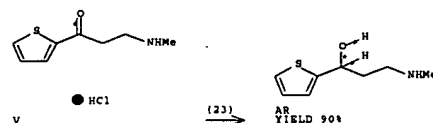
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO AQ 851878-67-6

RX(23) OF 74 ...V ==> AR



RX(23) RCT V 645411-16-1

STAGE(1)

RGT Z 16940-66-2 NaBH4
 SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) 1 hour, room temperature

STAGE(2)

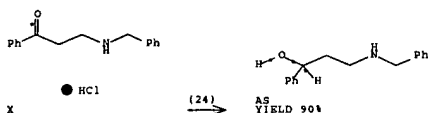
RGT AA 12125-02-9 NH4Cl
 SOL 7732-18-5 Water
 CON room temperature

STAGE(3)

RGT AB 1310-73-2 NaOH
 SOL 7732-18-5 Water
 CON room temperature, basify

PRO AR 116539-56-1

RX(24) OF 74 ...X ==> AS...



RX(24) RCT X 35274-92-1

STAGE(1)

RGT Z 16940-66-2 NaBH4
 SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) 1 hour, room temperature

STAGE(2)

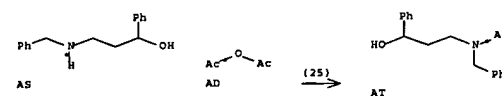
RGT AA 12125-02-9 NH4Cl
 SOL 7732-18-5 Water
 CON room temperature

STAGE(3)

RGT AB 1310-73-2 NaOH
 SOL 7732-18-5 Water
 CON room temperature, basify

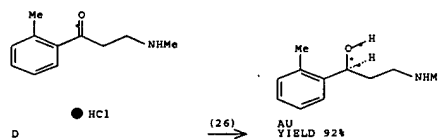
PRO AS 34597-73-4

RX(25) OF 74 ...AS + AD ==> AT



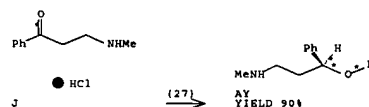
RX(25) RCT AS 34597-73-4, AD 108-24-7
 PRO AT 851878-69-8
 SOL 75-09-2 CH2Cl2
 CON 10 minutes, 0 deg C

RX(26) OF 74 ...D ==> AU



RX(26) RCT D 851878-34-7
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO AU 851878-71-2
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective, optimization study(optimized on reagent, solvent, pressure)

RX(27) OF 74 ...J ==> AY...



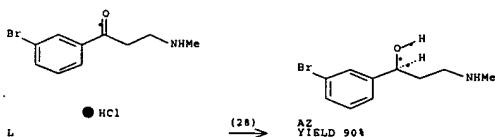
41

42

RX(27) RCT J 2538-50-3

RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO AY 114133-37-8
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

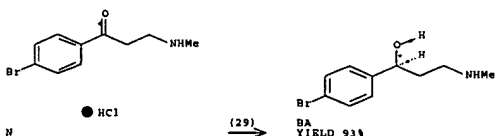
RX(28) OF 74 ...L ==> AZ



RX(28) RCT L 851878-36-9

RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO AZ 851878-74-5
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(29) OF 74 ...N ==> BA

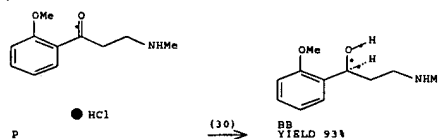


RX(29) RCT N 851878-38-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2

PRO BA 851878-76-7

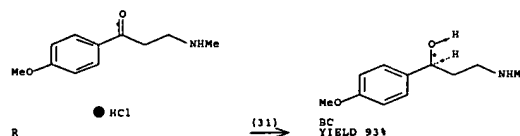
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(30) OF 74 ...P ==> BB



RX(30) RCT P 851878-40-5
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BB 851878-78-9
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(31) OF 74 ...R ==> BC



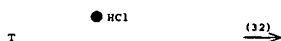
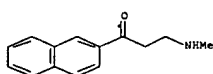
RX(31) RCT R 24206-62-0
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BC 851878-80-3
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-,

43

44

(OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

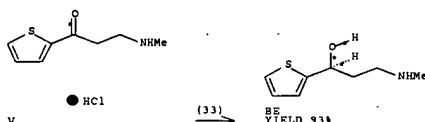
RX(32) OF 74 ...T ==> BD



BD
 YIELD 92%

RX(32) RCT T 645411-21-8
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BD 851878-82-5
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(33) OF 74 ...V ==> BE...

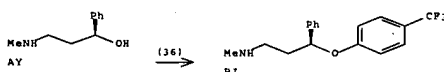


BE
 YIELD 93%

45

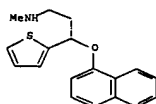
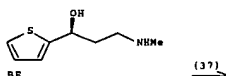
2,5-diene) [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(36) OF 74 ...AY ==> BI



RX(36) RCT AY 114133-37-8
 PRO BI 100568-02-3
 NTE literature preparation

RX(37) OF 74 ...BE ==> BJ



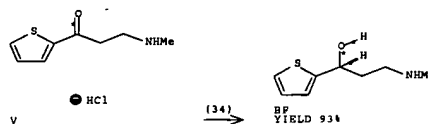
BJ

RX(37) RCT BE 116539-55-0
 PRO BJ 116539-59-4
 NTE literature preparation

L27 ANSWER 3 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 140:423470 CASREACT Full-text
 TITLE: Synthesis of 3-aminomethyl-1-propanol, a fluoxetine precursor
 INVENTOR(S): Zelenin, Alexander

RX(33) RCT V 645411-16-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BE 116539-55-0
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

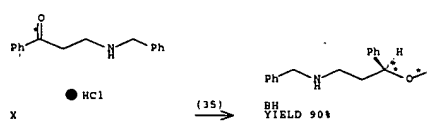
RX(34) OF 74 ...V ==> BF



BF
 YIELD 93%

RX(34) RCT V 645411-16-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BF 116539-57-2
 CAT 850780-91-5 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1R,1'R,2R,2'R)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(35) OF 74 ...X ==> BH



BH
 YIELD 90%

RX(35) RCT X 35274-92-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BH 851878-86-9
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-

46

10/520362

10/520362

PATENT ASSIGNER(S): Board of Regents, the University of Texas System, USA
 SOURCE: U.S. Pat. Appl. Publ., 7 pp.
 CODEN: USXXCO

DOCUMENT TYPE: Patent
 LANGUAGE: English
 INT. PATENT CLASSIF.: C07C225-10
 MAIN: 564343000
 US PATENT CLASSIF.: 25-9 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 CLASSIFICATION: Section cross-reference(s): 45, 63

FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004102651	A1	20040527	US 2002-302806	20021122
US 6846957	B2	20050125	US 2002-302806	20021122

PRIORITY APPLN. INFO.:

ABSTRACT:

Fluoxetine hydrochloride is prepared by: (a) synthesizing 1-phenyl-3-methylamino-1-propen-1-one by (i) the claisen condensation of acetophenone with Et formate leading to benzoylacetalddehyde sodium salt, and (ii) the condensation of the benzoylacetalddehyde sodium salt with methylamine hydrochloride; (b) converting 1-phenyl-3-methylamino-2-propen-1-one into 3-methylamino-1-phenyl-1-propanol using sodium borohydride and acetic acid; and (c) converting 3-methylamino-1-phenyl-1-propanol into fluoxetine hydrochloride by treatment with hydrochloric acid.

SUPPL. TERM: fluoxetine hydrochloride prepn; aminomethylpropanol prepn
 INDEX TERM: Condensation reaction

(Claisen; of acetophenone with Et formate to give benzoylacetalddehyde sodium salt)

INDEX TERM: Reduction
 (of 1-phenyl-3-methylamino-1-propen-1-one into 3-methylamino-1-phenyl-1-propanol with NaBH4 in AcOH)

INDEX TERM: Condensation reaction
 (of benzoylacetalddehyde sodium salt with methylamine hydrochloride to give 1-phenyl-3-methylamino-1-propen-1-one)

INDEX TERM: Neutralization
 (of fluoxetine with HCl in ether in the preparation of fluoxetine hydrochloride)

INDEX TERM: Ethers, uses
 ROLE: NUU (Other use, unclassified); USES (Uses)

(solvents; for the salification of fluoxetine with HCl)

INDEX TERM: 64-19-7, Acetic acid, uses
 ROLE: NUU (Other use, unclassified); USES (Uses)

(in the preparation of fluoxetine hydrochloride)

INDEX TERM: 98-56-6, 4-Chlorobenzotrifluoride 98-86-2, Acetophenone, reactions 109-94-4, Ethyl formate 593-51-1, Methylamine hydrochloride 1310-73-2, Sodium hydroxide, reactions 7647-01-0, Hydrogen chloride, reactions 16940-66-2, Sodium borohydride

ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (in the preparation of fluoxetine hydrochloride)

INDEX TERM: 877-50-9P 20717-88-8P, Benzoylacetalddehyde sodium salt 42142-52-9P, 3-Methylamino-1-phenyl-1-propanol

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

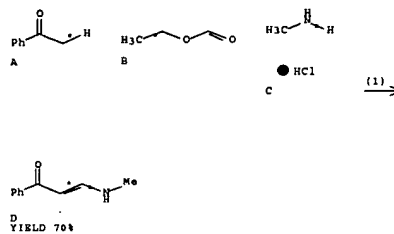
47

48

(in the preparation of fluoxetine hydrochloride)
 INDEX TERM: 54910-89-3P
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)
 INDEX TERM: 56296-78-7P, Fluoxetine hydrochloride
 ROLE: SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of)
 INDEX TERM: 67-68-5, DMSO, uses
 ROLE: MUU (Other use, unclassified); USES (Uses)
 (solvent; in the preparation of fluoxetine hydrochloride)
 REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD.
 REFERENCE(S): (1) Ager; Tet. Asymmetry 1997, V8(20), P3327 CAPLUS
 (2) Anon; GB 2060618 1981 CAPLUS
 (3) Anon; EP 0380924 1990 CAPLUS
 (4) Anon; FI 81083 1990 CAPLUS
 (5) Anon; EP 0457559 1991 CAPLUS
 (6) Anon; EP 0528842 1993 CAPLUS
 (7) Anon; HU 207035 1993
 (8) Anon; WO 9309769 1993 CAPLUS
 (9) Anon; WO 9400416 1994 CAPLUS
 (10) Anon; ES 2101650 1997 CAPLUS
 (11) Anon; ES 2103681 1997 CAPLUS
 (12) Anon; WO 9811054 1998 CAPLUS
 (13) Anon; WO 9905129 1999 CAPLUS
 (14) Anon; WO 9906362 1999 CAPLUS
 (15) Anon; WO 9967196 1999 CAPLUS
 (16) Anon; WO 0/21917 2000 CAPLUS
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 (18) Anon; WO 0037425 2000 CAPLUS
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 (42) Robertson; J. Labeled Compound Radiopharm. 1987, V24, P1397 CAPLUS
 (43) Robertson; J. Med. Chem. 1988, V31, P1412 CAPLUS
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 (45) Sakuraba; Syn. Lett. 1991, P689 CAPLUS

(46) Schwartz; 1993
 (47) Schwartz; US 5225585 A 1993 CAPLUS
 (48) Theriot; 1998
 (49) Theriot; US 5760243 A 1998 CAPLUS
 (50) Theriot; 1999
 (51) Weber; 2000
 (52) Wirth; Organic Proc. Res. Dev. 2000, V4, P513 CAPLUS
 (53) Young; 1992
 (54) Young; US 5104899 A 1992 CAPLUS
 (55) Young; 1993
 (56) Young; US 5708035 A 1998 CAPLUS

RX(1) OF 9 A + B + C ==> D...



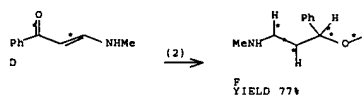
RX(1) RCT A 98-86-2, B 109-94-4

STAGE(1)
 CON room temperature

STAGE(2)
 RCT C 593-51-1
 SOL 7732-18-5 Water
 CON room temperature

PRO D 877-50-9
 NTE limited exptl. details, Claisen condensation

RX(2) OF 9 ...D ==> F...



49

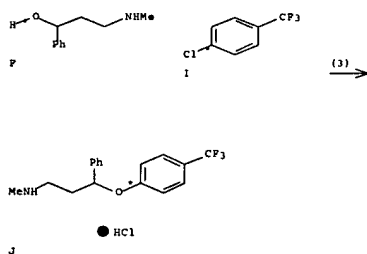
50

10/520362

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RX(2) RCT D 877-50-9
 RGT G 16940-66-2 NaBH4
 PRO F 42142-52-9
 SOL 64-19-7 AcOH
 CON SUBSTAGE(1) 30 minutes, 5 - 10 deg C
 SUBSTAGE(2) 30 minutes, 5 - 10 deg C
 SUBSTAGE(3) 3 hours, room temperature

RX(3) OF 9 ...F + I ==> J



RX(3) RCT F 42142-52-9

STAGE(1)
 RGT K 7646-69-7 NaH
 SOL 67-68-5 DMSO
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) 1 hour, room temperature -> 60 deg C

STAGE(2)
 RCT I 98-56-6
 CON SUBSTAGE(2) 6 hours, 115 deg C
 SUBSTAGE(3) 115 deg C -> room temperature

STAGE(3)
 RGT E 7732-18-5 Water

STAGE(4)
 RGT L 7647-01-0 HCl
 SOL 60-29-7 Et2O
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) 30 minutes, room temperature

PRO J 56296-78-7

RX(4) RCT F 42142-52-9

STAGE(1)
 RGT K 7646-69-7 NaH
 SOL 67-68-5 DMSO
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) 1 hour, room temperature -> 60 deg C

STAGE(2)
 RCT I 98-56-6
 CON SUBSTAGE(2) 6 hours, 115 deg C
 SUBSTAGE(3) 115 deg C -> room temperature

STAGE(3)
 RGT E 7732-18-5 Water

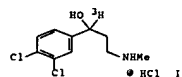
PRO O 54910-89-3

L27 ANSWER 4 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 114:5913 CASREACT Full-text
 TITLE: Synthesis of tritium labeled 1-(3,4-dichlorophenyl)-3-(methylamino)propanol hydrochloride
 AUTHOR(S): Hill, John A.; Wisowaty, James C.
 CORPORATE SOURCE: Chem. Dev. Lab., Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA
 SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1990), 28(7), 811-18
 CODEN: JLCRD4; ISSN: 0362-4803
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 CLASSIFICATION: 25-7 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 GRAPHIC IMAGE:

RX(4) OF 9 ...F + I ==> O

51

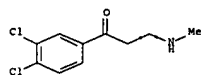
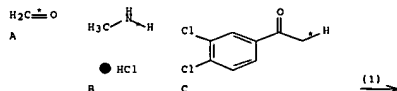
52



ABSTRACT:
1-(3,4-Dichlorophenyl)-3-(methylamino)-1-propanol hydrochloride, a potential antidepressant, was synthesized by a two-step method in the [3H]-labeled form I with specific activity 12.5 mCi/mmol suitable for drug metabolism and disposition studies.

SUPPL. TERM: chlorophenylmethylaminopropanol tritium labeled; propanol chlorophenylmethylamino tritium labeled
INDEX TERM: 2642-63-9
ROLE: RCT (Reactant); RACT (Reactant or reagent) (aminomethylation of)
INDEX TERM: 130826-97-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and reduction of)
INDEX TERM: 2538-50-3P 130826-98-1P 130826-99-2P 130827-00-8P
ROLE: SPN (Synthetic preparation); PREP (Preparation) (preparation of)

RX(1) OF 7 A + B + C ==> D...



D
YIELD 17%

RX(1) RCT A 50-00-0, B 593-51-1, C 2642-63-9
PRO D 130826-97-0

53

10/520362



J
YIELD 85%

RX(3) RCT D 130826-97-0
RGT G 16940-66-2 NaBH4
PRO J 130826-99-2
SOL 7732-18-5 Water, 67-63-0 Me2CHOH

RX(4) OF 7 ...D ==> L



L
YIELD 86%

RX(4) RCT D 130826-97-0
RGT G 16940-66-2 NaBH4, M 61113-34-6 NaBH3T
PRO L 130827-00-8
SOL 7732-18-5 Water, 67-63-0 Me2CHOH

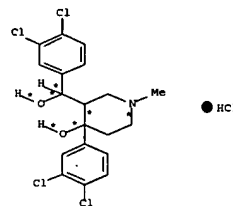
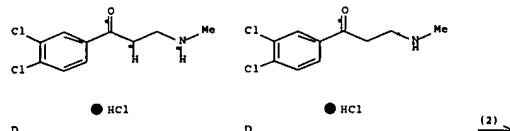
L27 ANSWER 5 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 108:6119 CASREACT Full-text
TITLE: Carbanion-accelerated Claisen rearrangements. 4. Asymmetric induction via 1,3,2-oxazaphosphorinanes
AUTHOR(S): Denmark, Scott S.; Marlin, John E.
CORPORATE SOURCE: Dep. Chem., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Journal of Organic Chemistry (1987), 52(26), 5742-5
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 29-7 (Organometallic and Organometalloidal Compounds)
GRAPHIC IMAGE:

55

SOL 64-17-5 EtOH

10/520362

RX(2) OF 7 ...2 D ==> F

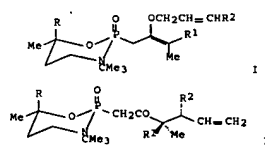


F
YIELD 48%

RX(2) RCT D 130826-97-0
RGT G 16940-66-2 NaBH4, H 7664-41-7 NH3
PRO F 130826-98-1
SOL 7732-18-5 Water

RX(3) OF 7 ...D ==> J

10/520362



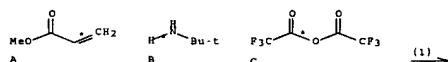
ABSTRACT:
The anions derived from allyl vinyl ethers I (R = Me; R1 = H, R2 = Me; R1 = R2 = H, Me) undergo rapid and highly selective Claisen rearrangements to give alkenyl ketone deriva. II. The degree of asym. induction is uniformly high (ca. 90:10) for various substituent patterns but depends markedly on the presence of lithium cations. The absolute sense of asym. induction has been established using chiral, nonracemic oxazaphosphorinane I (R = R2 = H). Two proposals for the transition structures of the phosphorus-stabilized anions are discussed.

SUPPL. TERM: Claisen rearrangement carbanion accelerated; asym induction Claisen rearrangement oxazaphosphorinane; allyl vinyl ether Claisen rearrangement; lithium cation asym Claisen rearrangement
INDEX TERM: Asymmetric synthesis and induction (in carbanion-accelerated Claisen rearrangement of allyl vinyl ethers via oxazaphosphorinanes)
INDEX TERM: Ethers, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent) (allyl vinyl, asym. carbanion-accelerated Claisen rearrangement of, via oxazaphosphorinane deriva.)
INDEX TERM: 96-33-3, Methyl 2-propenoate
ROLE: RCT (Reactant); RACT (Reactant or reagent) (addition of, to allenylphosphoramidate)
INDEX TERM: 504-61-0
ROLE: PROC (Process) (addition of, to allenylphosphoramidate)
INDEX TERM: 107-18-6, Allyl alcohol, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent) (addition of, to allenylphosphoramidate)
INDEX TERM: 7447-41-8, Lithium chloride, uses and miscellaneous
ROLE: USES (Uses) (asym. carbanion-accelerated Claisen rearrangement of oxazaphosphorinane derivative in presence of)
INDEX TERM: 111525-49-6P 111525-51-0P 111525-52-1P 111525-54-3P 111613-01-6P
ROLE: SPN (Synthetic preparation); PREP (Preparation) (asym. preparation of)
INDEX TERM: 141-97-9
ROLE: RCT (Reactant); RACT (Reactant or reagent) (enantioselective yeast reduction of)
INDEX TERM: 111525-47-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and addition reaction of, with allyl alc.)
INDEX TERM: 111525-43-0P

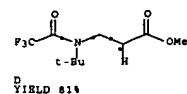
56

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and addition reaction of, with hydroxybutene)
INDEX TERM: 111525-42-9P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and addition reactions of, with allylic alca.)
INDEX TERM: 56816-01-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and amidation of)
INDEX TERM: 111525-44-1P 111525-45-2P 111525-46-3P 111525-48-5P 111612-96-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and asym. carbanion accelerated Claisen rearrangement of)
INDEX TERM: 111525-40-7P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and borane reduction of)
INDEX TERM: 111525-38-3P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with Grignard reagent)
INDEX TERM: 111525-41-8P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with trichlorophosphine and hydroxybutyne, allenylphosphoramidates from)
INDEX TERM: 111525-50-9P 111525-53-2P 111612-97-6P 111612-98-7P 111612-99-8P 111613-00-4P 111613-02-6P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
INDEX TERM: 7719-12-2, Trichlorophosphine
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with amino alca. and propargyl alca., allenylphosphoramidates from)
INDEX TERM: 115-19-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with trichlorophosphine and amino alca., allenylphosphoramidate from)
INDEX TERM: 2028-63-9, 3-Hydroxy-1-butyne
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with trichlorophosphine and amino alca., allenylphosphoramidates from)
INDEX TERM: 111525-39-4
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with trichlorophosphine and propargyl alca., allenylphosphorimidate from)

RX(1) OF 80 A + B + C ==> D...

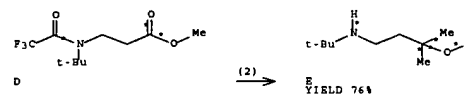


57



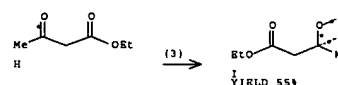
RX(1) RCT A 96-33-3, B 75-64-9
STAGE(1)
STAGE(2)
RCT C 407-25-0
PRO D 111525-38-3

RX(2) OF 80 ...D ==> E...



RX(2) RCT D 111525-38-3
RGT F 75-16-1 MeMgBr
PRO E 111525-39-4
SOL 60-29-7 Et2O

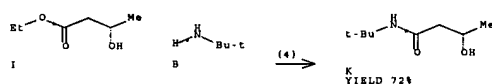
RX(3) OF 80 H ==> I...



RX(3) RCT H 141-97-9
PRO I 56816-01-4
SOL 7732-18-5 Water
NTE yeast

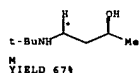
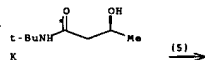
58

RX(4) OF 80 ...I + B ==> K...



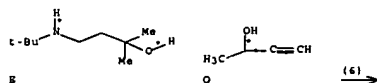
RX(4) RCT I 56816-01-4, B 75-64-9
RGT L 75-24-1 AlMe3
PRO K 111525-40-7

RX(5) OF 80 ...K ==> M...

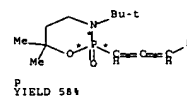


RX(5) RCT K 111525-40-7
RGT N 14044-65-6 BH3-THF
PRO M 111525-41-8

RX(6) OF 80 ...E + O ==> P...

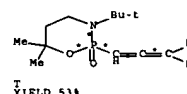
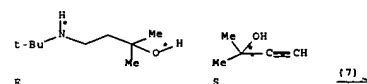


59



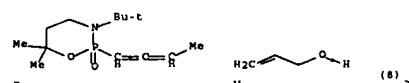
RX(6) RCT E 111525-39-4, O 2028-63-9
RGT Q 109-02-4 N-Methylmorpholine, R 7719-12-2 PC13
PRO P 111525-42-9

RX(7) OF 80 ...E + S ==> T...

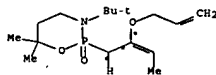


RX(7) RCT E 111525-39-4, S 115-19-5
RGT Q 109-02-4 N-Methylmorpholine, R 7719-12-2 PC13
PRO T 111525-43-0

RX(8) OF 80 ...P + U ==> V...



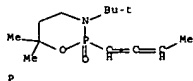
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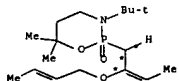
V
YIELD 64%

RX(8) RCT P 111525-42-9, U 107-18-6
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO V 111525-44-1
SOL 109-99-9 THF

RX(9) OF 80 ...P + Z ==> AA...



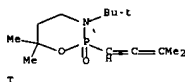
(9)



AA
YIELD 46%

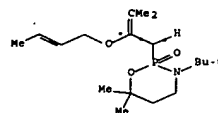
RX(9) RCT P 111525-42-9, Z 504-61-0
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AA 111525-45-2
SOL 109-99-9 THF

RX(10) OF 80 ...T + Z ==> AB...



(10)

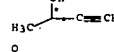
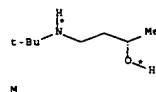
61



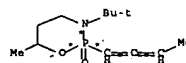
AB
YIELD 51%

RX(10) RCT T 111525-43-0, Z 504-61-0
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AB 111525-46-3
SOL 109-99-9 THF

RX(11) OF 80 ...M + O ==> AC...



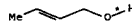
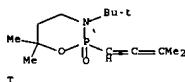
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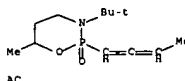
AC
YIELD 54%

RX(11) RCT M 111525-41-8, O 2028-63-9
RGT Q 109-02-4 N-Methylmorpholine, R 7719-12-2 PC13
PRO AC 111525-47-4

RX(12) OF 80 ...AC + U ==> AD...



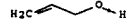
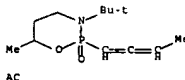
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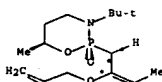
AD
YIELD 54%

RX(12) RCT AC 111525-47-4, U 107-18-6
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AD 111525-48-5
SOL 109-99-9 THF

RX(13) OF 80 ...AC + U ==> AE...



(13)

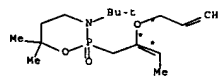


AE
YIELD 30%

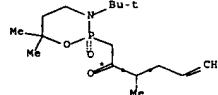
RX(13) RCT AC 111525-47-4, U 107-18-6
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AE 111612-96-5
SOL 109-99-9 THF

63

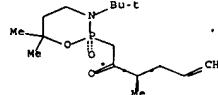
RX(14) OF 80 ...2 V ==> AF + AG



(14)



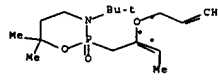
AF
YIELD 77% (52)



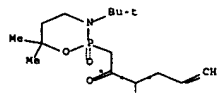
AG
YIELD 77% (48)

RX(14) RCT V 111525-44-1
RGT AH 7693-26-7 KH
PRO AF 111525-49-6, AG 111525-50-9
SOL 67-68-5 DMSO, 109-99-9 THF

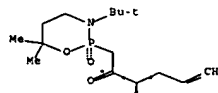
RX(15) OF 80 2 V ==> AF + AG



(15)



AF
YIELD 81% (91)

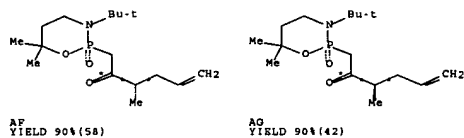
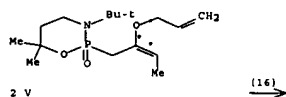


AG
YIELD 81% (9)

64

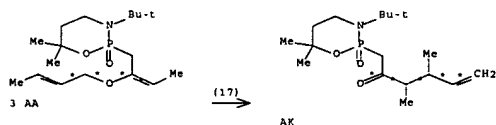
RX(15) RCT V 111525-44-1
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AF 111525-49-6, AG 111525-50-9
SOL 67-68-5 DMSO, 109-99-9 THF

RX(16) OF 80 2 V ==> AF + AG

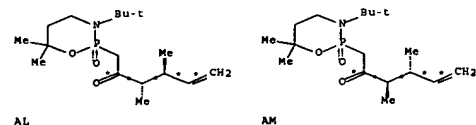


RX(16) RCT V 111525-44-1
PRO AF 111525-49-6, AG 111525-50-9
SOL 109-99-9 THF

RX(17) OF 80 ...3 AA ==> AK + AL + AM

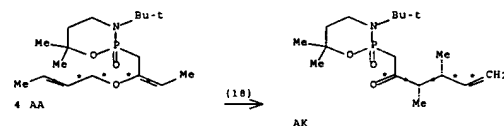


AK

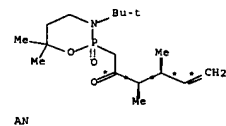
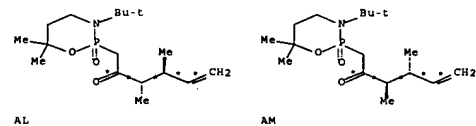


RX(17) RCT AA 111525-45-2
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AK 111525-51-0, AL 111612-97-6, AM 111612-98-7
SOL 67-68-5 DMSO, 109-99-9 THF
NTE 80% overall

RX(18) OF 80 ...4 AA ==> AK + AL + AM + AN



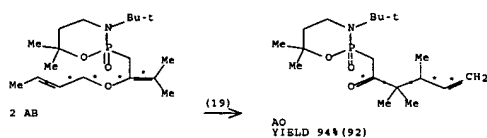
AK



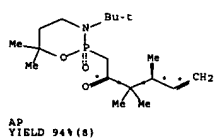
65

RX(18) RCT AA 111525-45-2
PRO AK 111525-51-0, AL 111612-97-6, AM 111612-98-7, AN 111612-99-8
SOL 109-99-9 THF
NTE 84% overall

RX(19) OF 80 ...2 AB ==> AO + AP

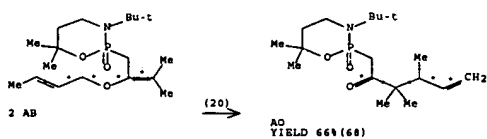


AO YIELD 94% (92)

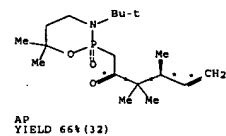


RX(19) RCT AB 111525-46-3
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AO 111525-52-1, AP 111525-53-2
SOL 67-68-5 DMSO, 109-99-9 THF

RX(20) OF 80 2 AB ==> AO + AP

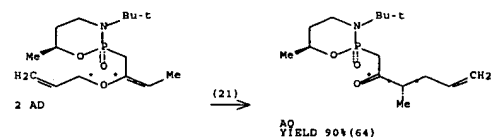


AO YIELD 66% (68)

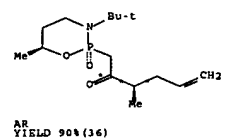


RX(20) RCT AB 111525-46-3
PRO AO 111525-52-1, AP 111525-53-2
SOL 109-99-9 THF

RX(21) OF 80 ...2 AD ==> AQ + AR



AQ YIELD 90% (64)



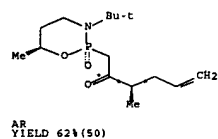
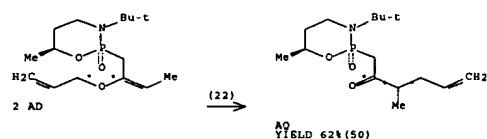
RX(21) RCT AD 111525-48-5
RGT AJ 7447-41-8 LiCl
PRO AQ 111525-54-3, AR 111613-00-4
SOL 109-99-9 THF

RX(22) OF 80 2 AD ==> AQ + AR

67

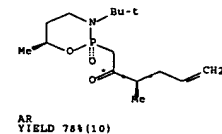
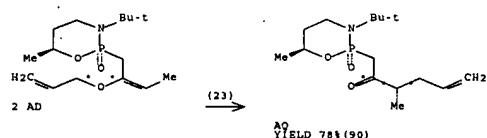
66

68



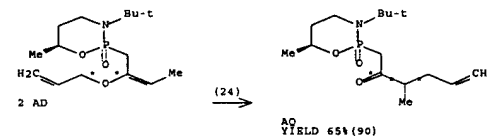
RX(22) RCT AD 111525-48-5
RGT AH 7693-26-7 KH
PRO AQ 111525-54-3, AR 111613-00-4
SOL 67-68-5 DMSO, 109-99-9 THF

RX(23) OF 80 2 AD ==> AQ + AR



RX(23) RCT AD 111525-48-5
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AQ 111525-54-3, AR 111613-00-4
SOL 67-68-5 DMSO, 109-99-9 THF

RX(24) OF 80 2 AD ==> AQ + AR

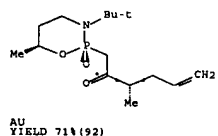
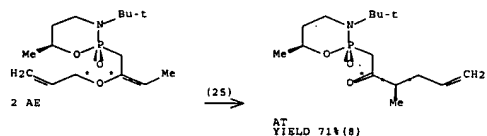


RX(24) RCT AD 111525-48-5
RGT AS 109-72-8 BuLi
PRO AQ 111525-54-3, AR 111613-00-4
SOL 67-68-5 DMSO, 109-99-9 THF

RX(25) OF 80 ... 2 AB ==> AT + AU

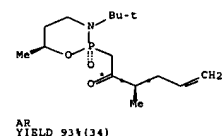
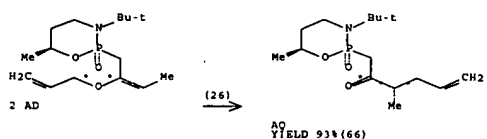
69

70



RX(25) RCT AB 111612-96-5
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AT 111613-01-5, AU 111613-02-6
SOL 67-68-5 DMSO, 109-99-9 THF

RX(26) OF 80 2 AD ==> AQ + AR



RX(26) RCT AD 111525-48-5
PRO AQ 111525-54-3, AR 111613-00-4
SOL 109-99-9 THF

L27 ANSWER 6 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 102:46134 CASREACT Full-text
TITLE: Herbicidal α -hydroxy phosphonates
INVENTOR(S): Gaertner, Van R.
PATENT ASSIGNER(S): Monsanto Co., USA
SOURCE: U.S., 9 pp. Division of U.S. 4,413,125.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.: A01N057-20
US PATENT CLASSIF.: 071086000
CLASSIFICATION: 29-7 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 5
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

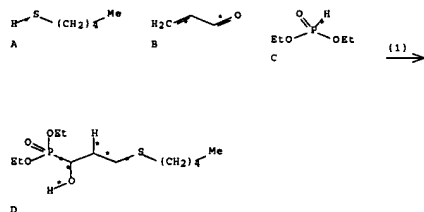
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4475943	A	19841009	US 1983-528700	19830901
US 4413125	A	19831101	US 1981-279371	19810701
			US 1981-279371	19810701

PRIORITY APPLN. INFO.: MARPAT 102:46134
OTHER SOURCE(S):
ABSTRACT:
(RO) (R1O) P(O) CR2(OH) CHR3CR4R5 (R,R1 = alkyl, CH2Ph; R2,R3,R4,R7 = H, alkyl; R5 = piperidinyl, XR6, NR7R8; R6 = alkyl, alkanoyl, aryl; R8 = alkyl, alkoxyalkyl; X = S, O) were prepared. Thus Me(CH2)4SH was treated with H2C:CHCHO and (EtO)2PH to give 80% Me(CH2)4SCH2CH2CH(OH)P(O)(OEt)2 (I). At 56.0 kg/ha, postemergent, I gave complete control of Chenopodium album (lambsquarters).

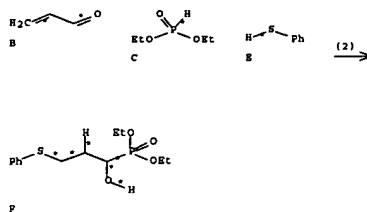
SUPPL. TERM: hydroxy phosphonate herbicide prepn
INDEX TERM: Herbicides
(phosphonates, α -hydroxy)
INDEX TERM: 89222-47-9P 89222-48-0P 89222-49-1P 89222-50-4P
89222-51-5P 89222-52-6P 89222-53-7P 89222-54-8P
89222-55-9P 89222-56-0P 89222-57-1P 89222-59-3P
89222-60-6P 94128-48-0P
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and herbicidal activity of)

INDEX TERM: 89222-61-7P 89222-62-8P
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)
 INDEX TERM: 868-85-9
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein)
 INDEX TERM: 762-04-9
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein and amines or mercaptans)
 INDEX TERM: 60-24-2 74-85-1, reactions 75-33-2 75-64-9, reactions
 105-53-3 108-98-5, reactions 109-89-7, reactions
 110-66-7 110-89-4, reactions 111-92-2 594-39-8
 1639-09-4
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein and di-Et phosphite)
 INDEX TERM: 17176-77-1
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein and diethylamine)
 INDEX TERM: 107-03-9
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with carbonyl compds. and di-Et phosphite)
 INDEX TERM: 107-02-8, reactions
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with mercaptans or amines and di-Et
 phosphite)
 INDEX TERM: 78-85-3 78-94-4, reactions
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with propanethiol and di-Et phosphite)

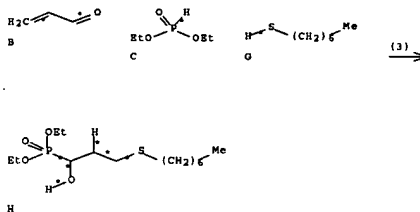
RX(1) OF 14 A + B + C ==> D

RX(1) RCT A 110-66-7, B 107-02-8, C 762-04-9
PRO D 89222-47-9

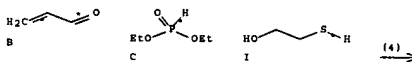
RX(2) OF 14 B + C + E ==> F

RX(2) RCT B 107-02-8, C 762-04-9, E 108-98-5
PRO F 89222-48-0

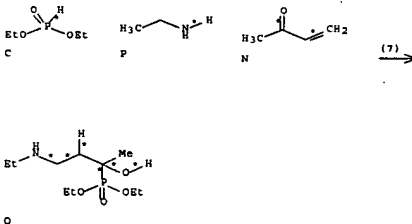
RX(3) OF 14 B + C + G ==> H

RX(3) RCT B 107-02-8, C 762-04-9, G 1639-09-4
PRO H 89222-49-1

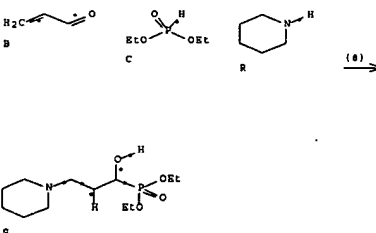
RX(4) OF 14 B + C + I ==> J

RX(6) RCT C 762-04-9, M 107-03-9, N 78-94-4
PRO O 89222-53-7

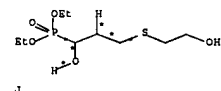
RX(7) OF 14 C + P + N ==> Q

RX(7) RCT C 762-04-9, P 75-04-7, N 78-94-4
PRO Q 89222-54-8

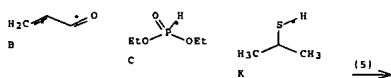
RX(8) OF 14 B + C + R ==> S

RX(8) RCT B 107-02-8, C 762-04-9, R 110-89-4
PRO S 89222-55-9

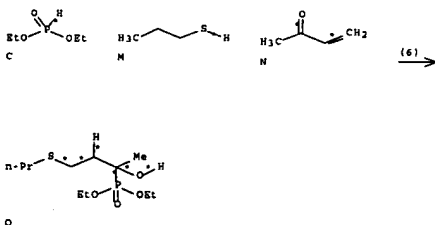
RX(9) OF 14 B + C + T ==> U

RX(4) RCT B 107-02-8, C 762-04-9, I 60-24-2
PRO J 89222-50-4

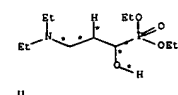
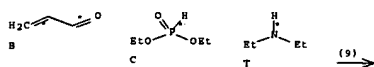
RX(5) OF 14 B + C + K ==> L

RX(5) RCT B 107-02-8, C 762-04-9, K 75-33-2
PRO L 89222-51-5

RX(6) OF 14 C + M + N ==> O

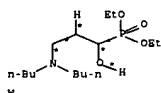
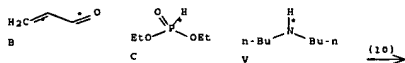


RX(9) OF 14 B + C + T ==> U



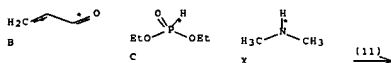
RX(9) RCT B 107-02-8, C 762-04-9, T 109-89-7
PRO U 89222-56-0

RX(10) OF 14 B + C + V ==> W

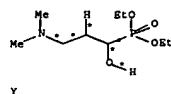


RX(10) RCT B 107-02-8, C 762-04-9, V 111-92-2
PRO W 89222-59-3

RX(11) OF 14 B + C + X ==> Y

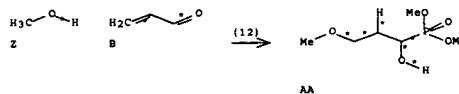


77



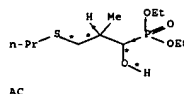
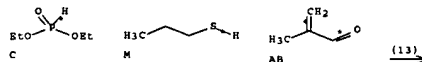
RX(11) RCT B 107-02-8, C 762-04-9, X 124-40-3
PRO Y 94128-48-0

RX(12) OF 14 Z + B ==> AA



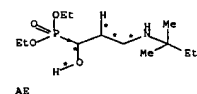
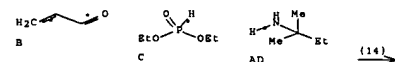
RX(12) RCT Z 67-56-1, B 107-02-8
PRO AA 89222-62-8

RX(13) OF 14 C + M + AB ==> AC



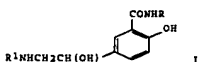
RX(13) RCT C 762-04-9, M 107-03-9, AB 78-85-3
PRO AC 89222-52-6

RX(14) OF 14 B + C + AD ==> AE



RX(14) RCT B 107-02-8, C 762-04-9, AD 594-39-8
PRO AE 89222-57-1

L27 ANSWER 7 OF 8 CASREACT COPYRIGHT 2007 ACS ON STN
ACCESSION NUMBER: 96:199236 CASREACT [Full-Text](#)
TITLE: Arylethanolamines derived from salicylamide with
alpha- and beta-adrenoceptor blocking activities.
Preparation of labetalol, its enantiomers and related
salicylamides
AUTHOR(S): Clifton, James S.; Collins, Ian; Hallett, Peter;
Hartley, David; Lunts, Lawrence H. C.; Wicke, Philip
D.
CORPORATE SOURCE: Chem. Dep., Glaxo Group Res. Ltd., Ware/Herts., SG12
0DJ, UK
SOURCE: Journal of Medicinal Chemistry (1982), 25(6), 670-9
CODEN: JMCNAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 25-19 (Benzene, Its Derivatives, and Condensed
Benzenoid Compounds)
Section cross-reference(s): 1
GRAPHIC IMAGES:



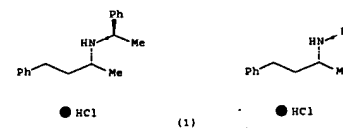
ABSTRACT:
Phenylethanolamines I (R = H, Me, PhCH₂, HOCH₂CH₂, NH₂; R₁ = alkyl or
substituted alkyl) were prepared and shown to possess beta-adrenergic blocking
properties. When the basic N atom was substituted by some aralkyl groups, the
comps. also blocked alpha-adrenoceptors. Labetalol (I; R = H, R₁ =
PhCH₂CH₂CH₂Me) is antihypertensive in animals and man, and syntheses of its 4

stereoisomers are described. The enantiomer with the (R) configuration at both
asym. centers possessed most of the beta-blocking activity but little
alpha-blocking activity. That with the (S) configuration at the alc. carbon
and the (R) configuration on the amino substituent is predominantly an
alpha-adrenoceptor blocking agent.

SUPPL. TERM: salicylamide ethanolamine deriv; labetalol stereoisomer
prepn antihypertensive
INDEX TERM: Antihypertensives
INDEX TERM: (labetalol enantiomers and related salicylamides as)
Isomerism and isomers
INDEX TERM: (of labetalol, antihypertensive activity and)
Molecular structure-biological activity relationship
(antihypertensive, of arylethanolamines derived from
salicylamide)
INDEX TERM: 24076-03-7 24076-19-5 81580-28-1
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(amidation of)
INDEX TERM: 24085-18-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(amidation of, or condensation with acetophenone and
formaldehyde)
INDEX TERM: 68164-04-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(amidation reaction, with (bromoacetyl)salicylamide)
INDEX TERM: 1611-38-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(catalytic hydrogenation of)
INDEX TERM: 104-53-0
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, (aminohydroxyethyl)salicylamide)
INDEX TERM: 98-86-2, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with [(aminohydroxyethyl)amino]ethyl
salicylate and formaldehyde)
INDEX TERM: 32780-66-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aldehydes and acetophenone)
INDEX TERM: 103-79-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aminoacetophenone derivative)
INDEX TERM: 78-95-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aniline derivative)
INDEX TERM: 2627-86-3 3886-69-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with benzylacetone)
INDEX TERM: 73866-23-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with benzylamine derivative, and amidation
of)
INDEX TERM: 2550-26-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with alpha-methylbenzylamine)
INDEX TERM: 75659-08-4P 81602-13-3P 81602-14-4P 81602-15-5P
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic
preparation); TRU (Therapeutic use); BIOLO (Biological
study); PREP (Preparation); USES (Uses)

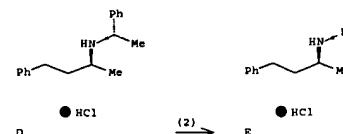
INDEX TERM: (preparation and antihypertensive activity of)
32780-63-5P 36256-61-8P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and catalytic hydrogenation of)
INDEX TERM: 80744-23-6P 81580-35-0P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and condensation with (bromoacetyl)salicylamide)
INDEX TERM: 81580-36-1P 81580-38-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrogenation-benzoylation of)
INDEX TERM: 24076-04-8P 24076-14-0P 75615-55-3P 75615-56-4P
81580-32-7P 81580-33-8P 81580-37-2P 81585-06-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrogenolysis of)
INDEX TERM: 72487-35-5P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and resolution of racemic)
INDEX TERM: 826-16-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-benzoylation of)
INDEX TERM: 24076-05-9P 24076-10-6P 24076-11-7P 24076-12-8P
24076-13-9P 24076-15-1P 24076-21-9P 24084-97-7P
25034-32-6P 32780-35-1P 32780-39-5P 32780-69-1P
32780-70-4P 32780-71-5P 32780-72-6P 32780-73-7P
36256-60-7P 36270-45-8P 54646-15-0P 56290-92-7P
63416-60-4P 63416-61-5P 63416-66-0P 64449-93-0P
64450-21-1P 64450-22-2P 64779-91-5P 64779-92-6P
64779-93-7P 70161-10-3P 72371-11-0P 75659-07-3P
81579-44-4P 81579-45-5P 81579-46-6P 81579-47-7P
81579-48-8P 81579-49-9P 81579-50-2P 81579-51-3P
81579-52-4P 81579-54-6P 81579-55-7P 81579-56-8P
81579-57-9P 81579-58-0P 81579-59-1P 81579-60-4P
81580-04-3P 81580-05-4P 81580-06-5P 81580-07-6P
81580-08-7P 81580-09-8P 81580-10-1P 81580-11-2P
81580-12-3P 81580-13-4P 81580-14-5P 81580-15-6P
81580-16-7P 81580-17-8P 81580-18-9P 81580-19-0P
81580-20-3P 81580-21-4P 81580-22-5P 81580-23-6P
81580-24-7P 81580-25-8P 81580-26-9P 81580-27-0P
81580-29-2P 81580-30-5P 81580-31-6P 81580-34-9P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
INDEX TERM: 72487-34-4P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of enantiomeric components of racemic)
INDEX TERM: 459-59-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with chloropropanone)
INDEX TERM: 30566-92-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with phenylpropanone)

RX(1) OF 182 ...A ==> B...



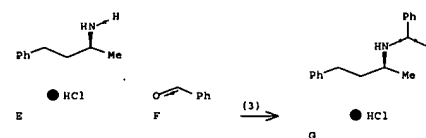
RX(1) RCT A 81580-32-7
PRO B 826-16-4
CAT 144-55-8 NaHCO₃

RX(2) OF 182 ...D ==> E...



RX(2) RCT D 81580-33-8
PRO E 81580-34-9
CAT 144-55-8 NaHCO₃

RX(3) OF 182 ...E + F ==> G...

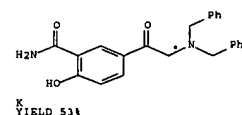
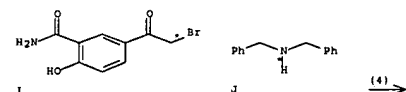


RX(3) RCT E 81580-34-9, F 100-52-7
RGT H 7647-01-0 HCl
PRO G 80744-23-6
CAT 144-55-8 NaHCO₃

81

82

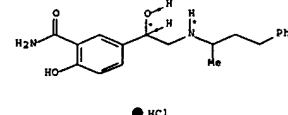
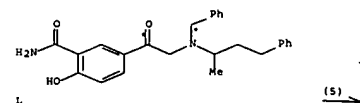
RX(4) OF 182 I + J ==> K...



YIELD 53%

RX(4) RCT I 73866-23-6, J 103-49-1
PRO K 30566-92-8

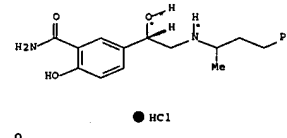
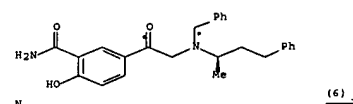
RX(5) OF 182 ...L ==> M



YIELD 67%

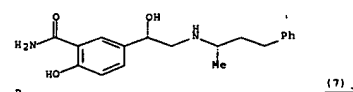
RX(5) RCT L 81579-50-2
RGT H 7647-01-0 HCl
PRO M 32780-64-6

RX(6) OF 182 ...N ==> O



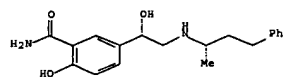
RX(6) RCT N 81580-36-1
PRO O 72487-34-4

RX(7) OF 182 ...P ==> Q



83

84

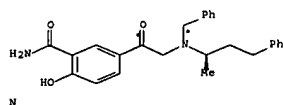


● HCl

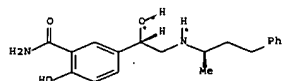
YIELD 87%

RX(7) RCT P 72487-32-2
RGT H 7647-01-0 HCl
PRO O 72487-34-4

RX(8) OF 182 ...N ==> Q



(8) →

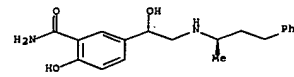


● HCl

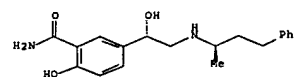
Q

RX(8) RCT N 81580-36-1
PRO Q 72487-35-5

RX(9) OF 182 ...R ==> Q



(9) →

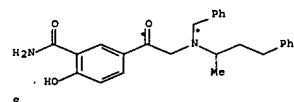


● HCl

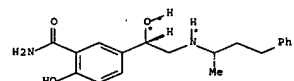
Q

RX(9) RCT R 72487-31-1
RGT H 7647-01-0 HCl
PRO Q 72487-35-5

RX(10) OF 182 ...S ==> Q



(10) →



● HCl

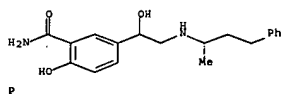
Q

85

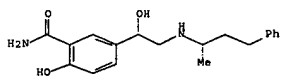
86

RX(10) RCT S 81580-38-3
PRO O 72487-34-4

RX(11) OF 182 P ==> O



(11) →

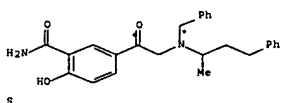


● HCl

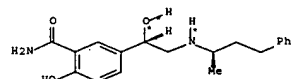
O

RX(11) RCT P 72487-32-2
RGT H 7647-01-0 HCl
PRO O 72487-34-4

RX(12) OF 182 ...S ==> Q



(12) →

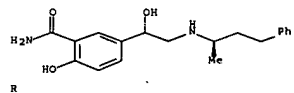


● HCl

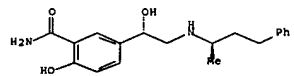
Q

RX(12) RCT S 81580-38-3
PRO Q 72487-35-5

RX(13) OF 182 R ==> Q



(13) →

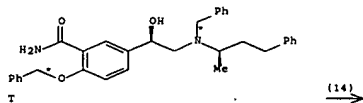


● HCl

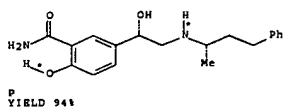
Q

RX(13) RCT R 72487-31-1
RGT H 7647-01-0 HCl
PRO Q 72487-35-5

RX(14) OF 182 T ==> P...

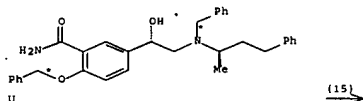


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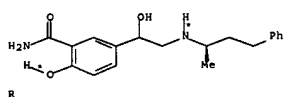


RX(14) RCT T 75615-55-3
PRO P 72487-32-2

RX(15) OF 182 U ==> R...

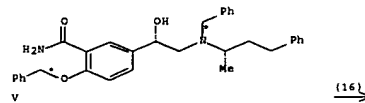


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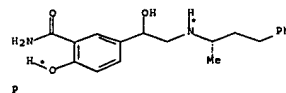


RX(15) RCT U 81580-37-2
PRO R 72487-31-1

RX(16) OF 182 V ==> P...

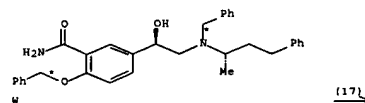


(16)

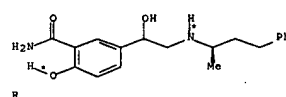


RX(16) RCT V 81585-06-0
PRO P 72487-32-2

RX(17) OF 182 W ==> R...



(17)

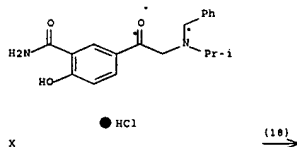


RX(17) RCT W 75615-56-4
PRO R 72487-31-1

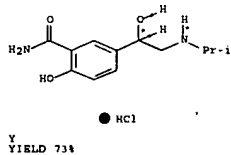
RX(18) OF 182 ...X ==> Y

89

90

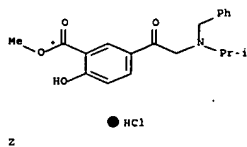


(18)

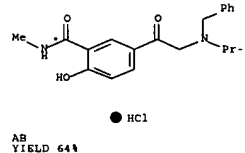


RX(18) RCT X 24076-04-8
PRO Y 24076-05-9

RX(19) OF 182 Z + AA ==> AB...

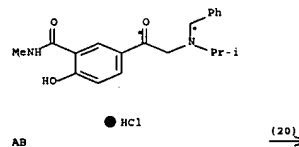


(19)

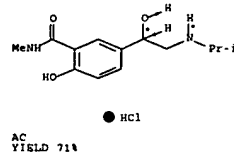


RX(19) RCT Z 24076-03-7, AA 74-89-5
PRO AB 24076-12-8

RX(20) OF 182 ...AB ==> AC



(20)

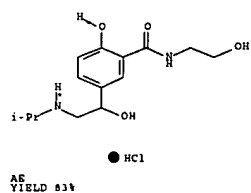
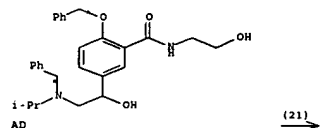


RX(20) RCT AB 24076-12-8
PRO AC 24076-13-9

RX(21) OF 182 ...AD ==> AE

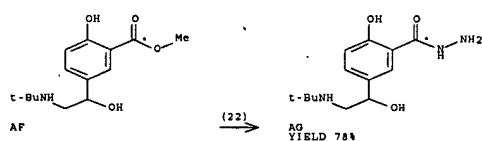
91

92



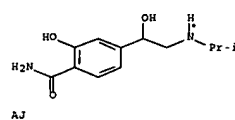
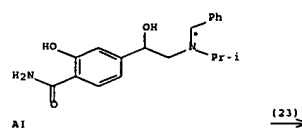
RX(21) RCT AD 344754-55-8
RGT H 7647-01-0 HCl
PRO AE 24076-21-9

RX(22) OF 182 AF ==> AG



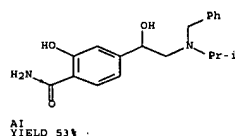
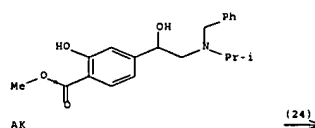
RX(22) RCT AF 27566-09-2
RGT AH 302-01-2 N2H4
PRO AG 24084-97-7

RX(23) OF 182 ...AI ==> AJ



RX(23) RCT AI 24076-14-0
PRO AJ 24076-15-1

RX(24) OF 182 AK ==> AI...

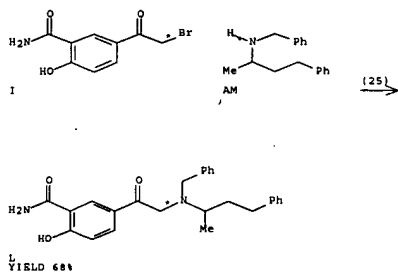


93

94

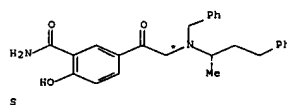
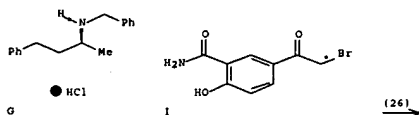
RX(24) RCT AK 81580-28-1
RGT AL 1336-21-6 NH4OH
PRO AI 24076-14-0

RX(25) OF 182 I + AM ==> L...



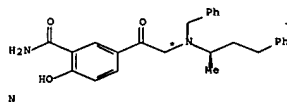
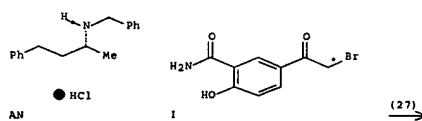
RX(25) RCT I 73866-23-6, AM 68164-04-5
PRO L 81579-50-2

RX(26) OF 182 ...G + I ==> S...



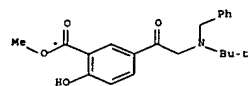
RX(26) RCT G 80744-23-6, I 73866-23-6
PRO S 81580-38-3
CAT 144-55-8 NaHCO3

RX(27) OF 182 ...AN + I ==> N...



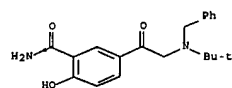
RX(27) RCT AN 81580-35-0, I 73866-23-6
PRO N 81580-36-1
CAT 144-55-8 NaHCO3

RX(28) OF 182 AO ==> AP...



● HCl

AO (28)

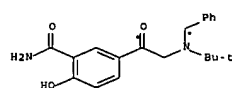


● HCl

AP
YIELD 80%

RX(28) RCT AO 27475-26-9
RGT AL 1336-21-6 NH4OH
PRO AP 36270-45-8

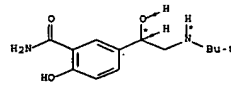
RX(29) OF 182 ...AP ==> AQ



● HCl

AP (29)

97

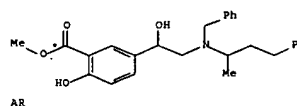


● HCl

AQ
YIELD 75%

RX(29) RCT AP 36270-45-8
PRO AQ 24076-10-6

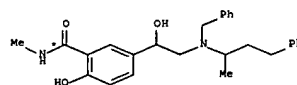
RX(30) OF 182 AR + AA ==> AS...



(30)

AR

AA



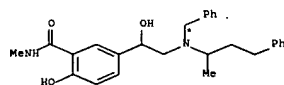
● HCl

AS

RX(30) RCT AR 345948-53-0, AA 74-89-5
PRO AS 81579-51-3

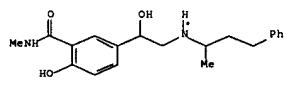
RX(31) OF 182 ...AS ==> AT

98



● HCl

AS (31)

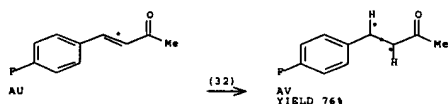


● HCl

AT
YIELD 28%

RX(31) RCT AS 81579-51-3
PRO AT 81580-27-0

RX(32) OF 182 AU ==> AV...



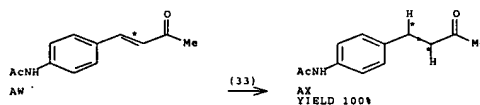
(32)

AV
YIELD 76%

RX(32) RCT AU 1611-38-7
PRO AV 63416-61-5

RX(33) OF 182 AW ==> AX...

99

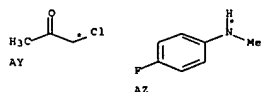


(33)

AX
YIELD 100%

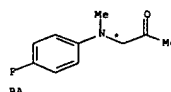
RX(33) RCT AW 27861-32-1
PRO AX 54646-15-0

RX(34) OF 182 AY + AZ ==> BA...



AZ

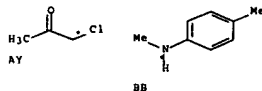
(34)



BA

RX(34) RCT AY 78-95-5, AZ 459-59-6
PRO BA 64450-21-1
CAT 144-55-8 NaHCO3

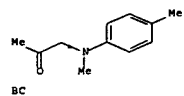
RX(35) OF 182 AY + BB ==> BC...



BB

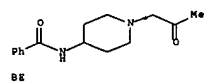
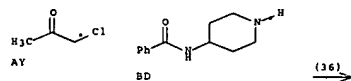
(35)

100



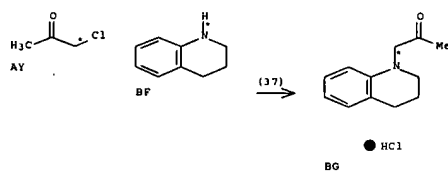
RX(35) RCT AY 78-95-5, BB 623-08-5
PRO BC 64450-22-2
CAT 144-55-8 NaHCO₃

RX(36) OF 182 AY + ED ==> BE...



RX(36) RCT AY 78-95-5, BD 33953-37-6
PRO BE 81580-30-5
CAT 144-55-8 NaHCO₃

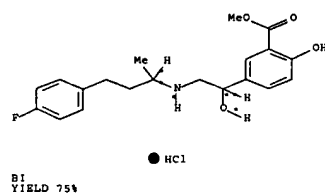
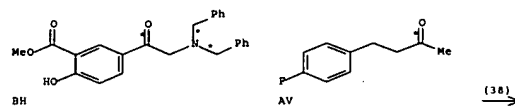
RX(37) OF 182 AY + BF ==> BG...



RX(37) RCT AY 78-95-5, BF 635-46-1

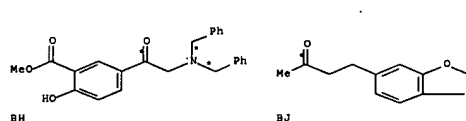
PRO BG 81580-31-6
CAT 144-55-8 NaHCO₃

RX(38) OF 182 ...BH + AV ==> BI...



RX(38) RCT BH 36270-04-9, AV 63416-61-5
RGT H 7647-01-0 HCl
PRO BI 63416-60-4

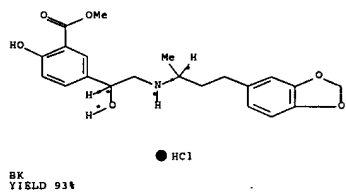
RX(39) OF 182 BH + BJ ==> BK...



(39)

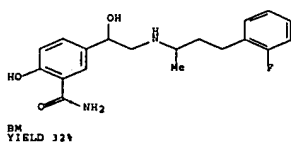
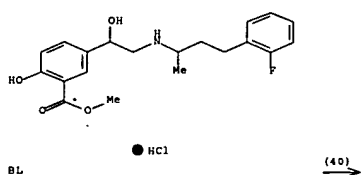
101

102



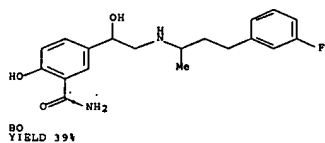
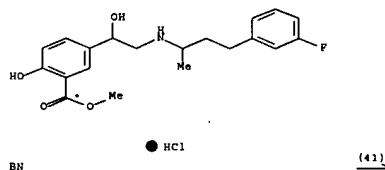
RX(39) RCT BH 36270-04-9, BJ 55418-52-5
RGT H 7647-01-0 HCl
PRO BK 56290-92-7

RX(40) OF 182 ...BL ==> BM



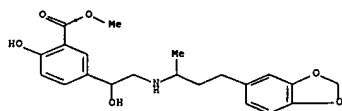
RX(40) RCT BL 63416-66-0
RGT AL 1336-21-6 NH₄OH
PRO BM 64779-92-6

RX(41) OF 182 BN ==> BO

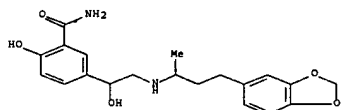


RX(41) RCT BN 63416-63-7
RGT AL 1336-21-6 NH₄OH
PRO BO 81580-09-8

RX(42) OF 182 ...BK ==> BP



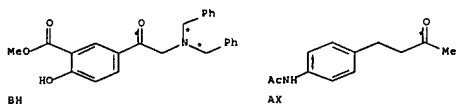
BK \bullet HCl $\xrightarrow{(42)}$



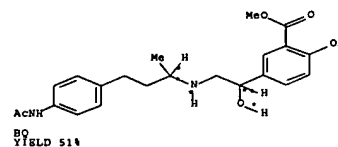
BP
YIELD 81%

RX(42) RCT BK 56290-92-7
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO BP 70161-10-3

RX(43) OF 182 ...BH + AX ==> BQ...

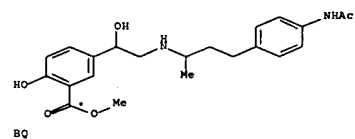


$\xrightarrow{(43)}$

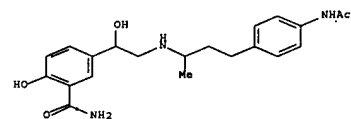


RX(43) RCT BH 36270-04-9, AX 54646-15-0
PRO BQ 81579-44-4

RX(44) OF 182 ...BQ ==> BR



BQ $\xrightarrow{(44)}$



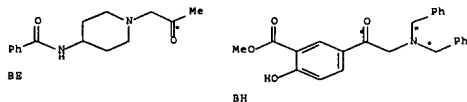
BR
YIELD 94%

RX(44) RCT BQ 81579-44-4
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO BR 81580-14-5

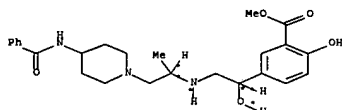
RX(45) OF 182 ...BE + BH ==> BS...

105

106



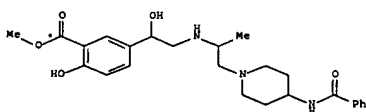
$\xrightarrow{(45)}$



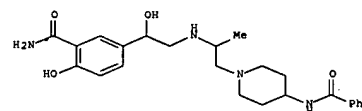
BS
YIELD 51%

RX(45) RCT BS 81580-30-5, BH 36270-04-9
PRO BS 81579-48-8

RX(46) OF 182 ...BS ==> BT



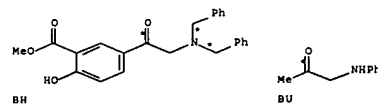
BT $\xrightarrow{(46)}$



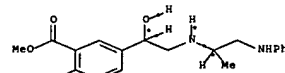
BT
YIELD 86%

RX(46) RCT BS 81579-48-8
RGT AL 1336-21-6 NH4OH
PRO BT 81579-57-9

RX(47) OF 182 BH + BU ==> BV...



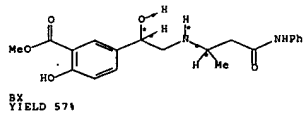
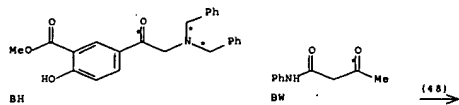
BH $\xrightarrow{(47)}$



BV
YIELD 84%

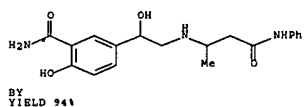
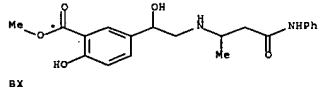
RX(47) RCT BH 36270-04-9, BU 4504-29-4
RGT H 7647-01-0 HCl
PRO BV 81579-49-9

RX(48) OF 182 BH + BW ==> BX...



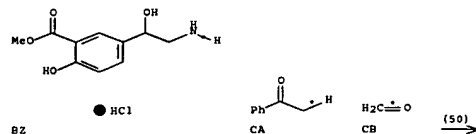
RX(48) RCT BH 36270-04-9, BW 102-01-2
PRO BX 64449-93-0

RX(49) OF 182 ...BX ==> BY



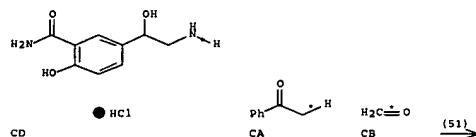
RX(49) RCT BX 64449-93-0
RGT AL 1336-21-6 NH4OH
PRO BY 81580-25-8

RX(50) OF 182 BZ + CA + CB ==> CC...



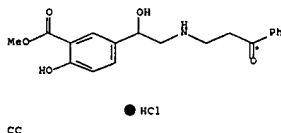
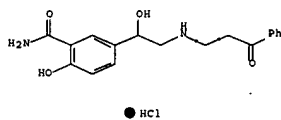
RX(50) RCT BZ 24085-18-5, CA 98-86-2, CB 50-00-0
PRO CC 81579-45-5

RX(51) OF 182 ...CD + CA + CB ==> CE



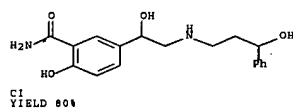
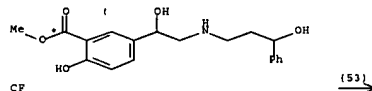
109

110



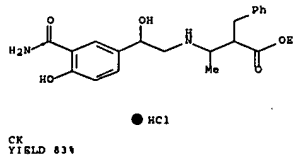
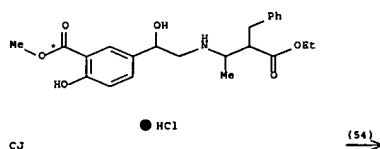
RX(52) RCT CC 81579-45-5
RGT CG 16949-15-8 LiBH4
PRO CF 81579-46-6
CAT 16940-66-2 NaBH4

RX(53) OF 182 ...CF ==> CI



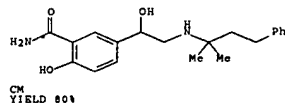
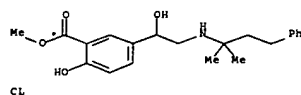
RX(53) RCT CF 81579-46-6
RGT AL 1336-21-6 NH4OH
PRO CI 81579-59-1

RX(54) OF 182 CJ ==> CK



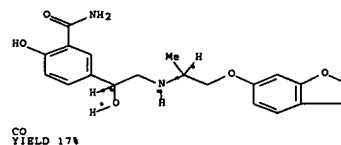
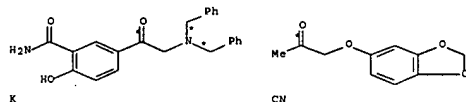
RX(54) RCT CJ 81579-47-7
RGT AL 1336-21-6 NH4OH
PRO CK 81579-58-0

RX(55) OF 182 CL ==> CM



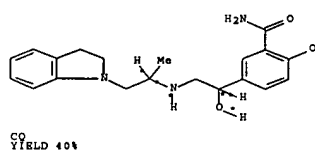
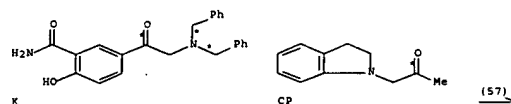
RX(55) RCT CL 345651-86-7
RGT AL 1336-21-6 NH4OH
PRO CM 32780-39-5

RX(56) OF 182 ...K + CN ==> CO



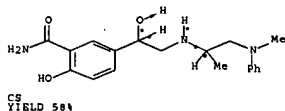
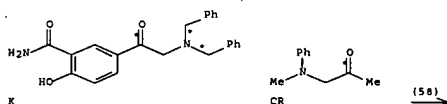
RX(56) RCT K 30566-92-8, CN 99807-06-4
PRO CO 81580-20-3

RX(57) OF 182 ...K + CP ==> CQ



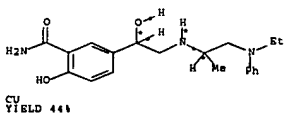
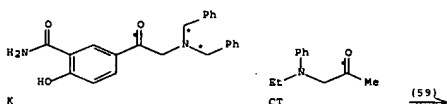
RX(57) RCT K 30566-92-8, CP 344304-70-7
PRO CQ 81579-55-7

RX(58) OF 182 ...K + CR ==> CS



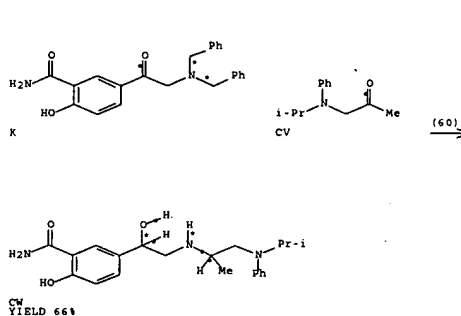
RX(58) RCT K 30566-92-8, CR 15885-06-0
PRO CS 72371-11-0

RX(59) OF 182 ...K + CT ==> CU



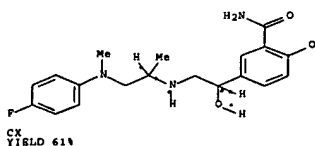
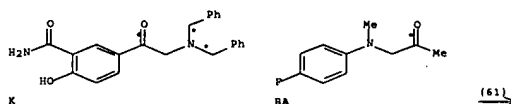
RX(59) RCT K 30566-92-8, CT 31199-19-6
PRO CU 81580-04-3

RX(60) OF 182 ...K + CV ==> CW



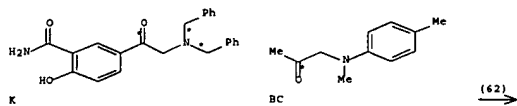
RX(60) RCT K 30566-92-8, CV 344308-74-3
PRO CW 81580-05-4

RX(61) OF 182 ...K + BA ==> CX



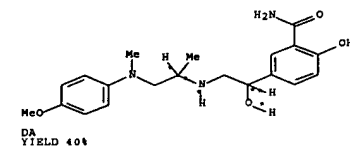
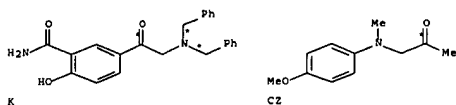
RX(61) RCT K 30566-92-8, BA 64450-21-1

RX(62) OF 182 ...K + BC ==> CY



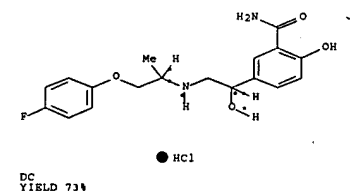
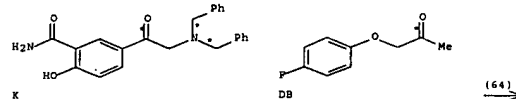
RX(62) RCT K 30566-92-8, BC 64450-22-2
PRO CY 81580-21-4

RX(63) OF 182 ...K + CZ ==> DA



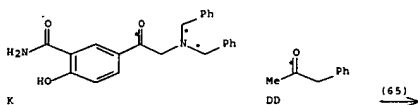
RX(63) RCT K 30566-92-8, CZ 64450-19-7
PRO DA 81580-24-7

RX(64) OF 182 ...K + DB ==> DC



RX(64) RCT K 30566-92-8, DB 81580-29-2
RGT H 7647-01-0 HCl
PRO DC 81580-19-0

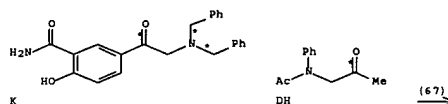
RX(65) OF 182 ...K + DD ==> DE



RX(65) RCT K 30566-92-8, DD 103-79-7
RGT H 7647-01-0 HCl
PRO DE 81579-52-4

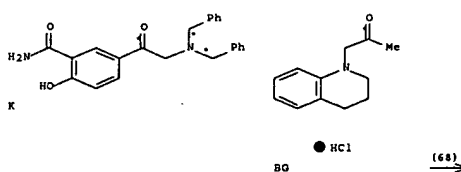
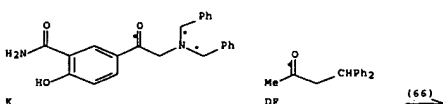
RX(66) RCT K 30566-92-8, DF 5409-60-9
RGT H 7647-01-0 HCl
PRO DG 32780-35-1

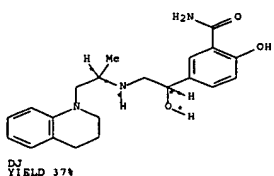
RX(67) OF 182 ...K + DH ==> DI



RX(67) RCT K 30566-92-8, DH 64450-18-6
RGT H 7647-01-0 HCl
PRO DI 81580-06-5

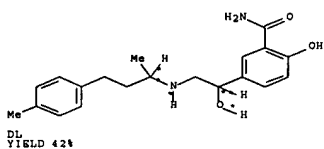
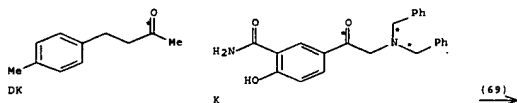
RX(68) OF 182 ...K + BG ==> DJ





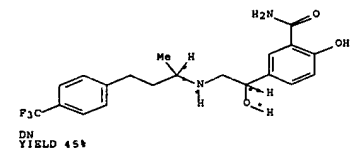
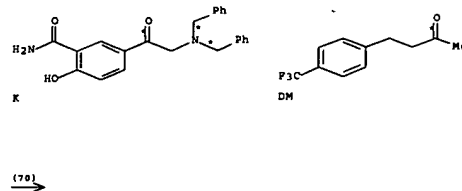
RX(68) RCT K 30566-92-8, BG 81580-31-6
PRO DJ 81579-56-8

RX(69) OF 182 ...DK + K ==> DL



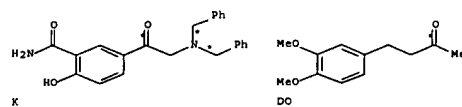
RX(69) RCT DK 7774-79-0, K 30566-92-8
PRO DL 81580-07-6

RX(70) OF 182 ...K + DM ==> DN



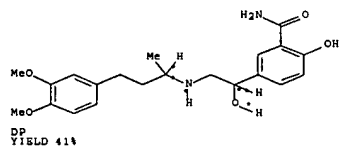
RX(70) RCT K 30566-92-8, DM 57132-19-1
PRO DN 81580-08-7

RX(71) OF 182 ...K + DO ==> DP



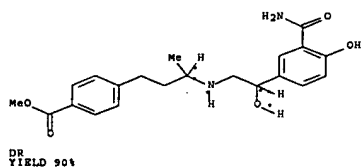
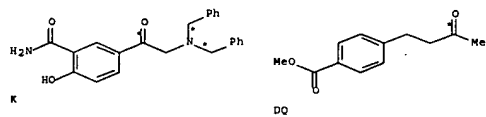
121

122



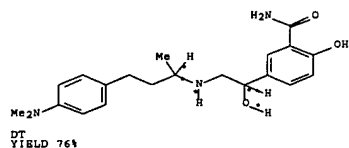
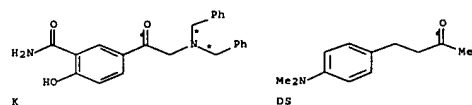
RX(71) RCT K 30566-92-8, DO 6302-60-9
PRO DP 81580-10-1

RX(72) OF 182 ...K + DQ ==> DR...



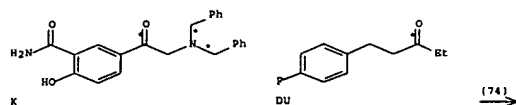
RX(72) RCT K 30566-92-8, DO 74248-99-0
PRO DR 81580-11-2

RX(73) OF 182 ...K + DS ==> DT



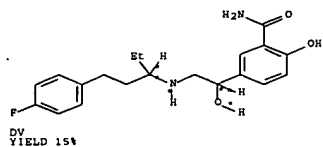
RX(73) RCT K 30566-92-8, DS 30780-30-4
PRO DT 81580-13-4

RX(74) OF 182 ...K + DU ==> DV



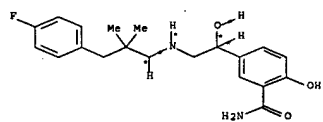
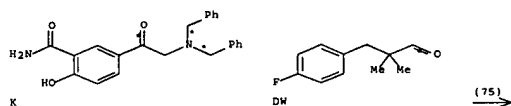
123

124



RX(74) RCT K 30566-92-8, DU 63416-75-1
PRO DV 81580-16-7

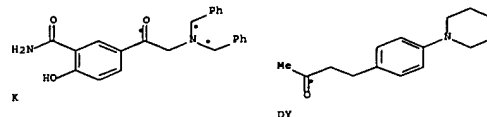
RX(75) OF 182 ...K + DW ==> DX



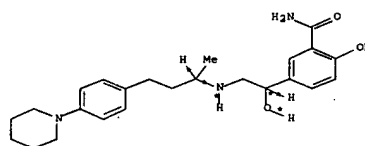
DX
YIELD 42%

RX(75) RCT K 30566-92-8, DW 4092-92-6
RGT H 7647-01-0 HCl
PRO DX 81580-17-8

RX(76) OF 182 ...K + DY ==> DZ



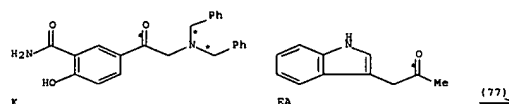
(76)



DZ
YIELD 27%

RX(76) RCT K 30566-92-8, DY 344304-03-6
RGT H 7647-01-0 HCl
PRO DZ 81580-15-6

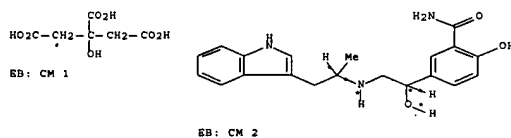
RX(77) OF 182 ...K + EA ==> EB



(77)

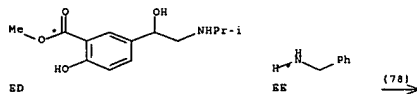
125

126

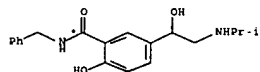


RX(77) RCT K 30566-92-8, EA 1201-26-9
PRO EB 81579-54-6
CAT 77-92-9 Citric acid

RX(78) OF 182 ED + ES ==> EF



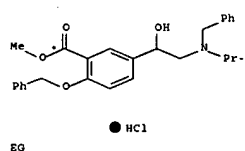
(78)



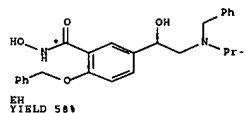
EF

RX(78) RCT ED 36270-12-9, ES 100-46-9
PRO EF 24076-11-7

RX(79) OF 182 EG ==> EH...

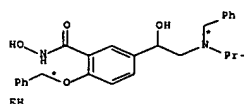


(79)

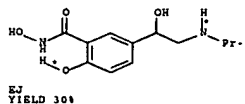


RX(79) RCT EG 24076-19-5
RGT EI 7803-49-8 NH2OH
PRO EH 36256-61-8

RX(80) OF 182 ...EH ==> EJ



(80)



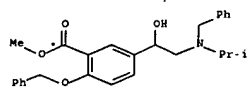
RX(80) RCT EH 36256-61-8

127

128

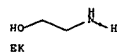
PRO EJ 36256-60-7

RX(81) OF 182 EG + EK ==> AD...



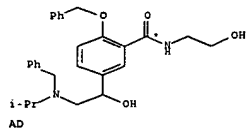
● HCl

EG



EK

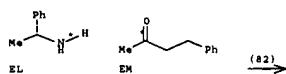
(81)



AD

RX(81) RCT EG 24076-19-5, EK 141-43-5
PRO AD 344754-55-8

RX(82) OF 182 EL + EM ==> A...



EL

● HCl

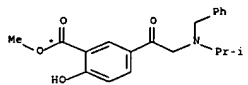
EM

(82)

129

PRO AN 81580-35-0
CAT 144-55-8 NaHCO₃

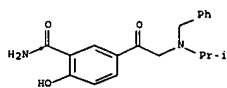
RX(85) OF 182 Z ==> X...



● HCl

Z

(85)

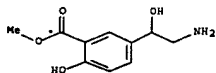


● HCl

X
YIELD 77%

RX(85) RCT Z 24076-03-7
RGT AL 1336-21-6 NH₄OH
PRO X 24076-04-8

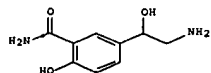
RX(86) OF 182 BZ ==> CD...



● HCl

BZ

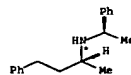
(86)



● HCl

CD
YIELD 62%

131

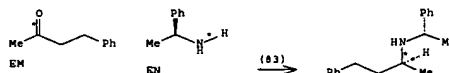


● HCl

A
YIELD 37%

RX(82) RCT EL 3886-69-9, EM 2550-26-7
RGT H 7647-01-0 HCl
PRO A 81580-32-7

RX(83) OF 182 EM + EN ==> D...

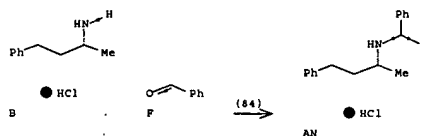


● HCl

D
YIELD 43%

RX(83) RCT EM 2550-26-7, EN 2627-86-3
RGT H 7647-01-0 HCl
PRO D 81580-33-8

RX(84) OF 182 ...B + F ==> AN...



● HCl

B

F

(84)

AN

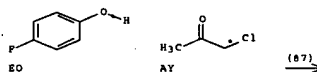
RX(84) RCT B 826-16-4, F 100-52-7
RGT H 7647-01-0 HCl

130

10/520362

RX(86) RCT BZ 24085-18-5
RGT AL 1336-21-6 NH₄OH
PRO CD 32780-65-7

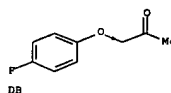
RX(87) OF 182 EO + AY ==> DB...



EO

AY

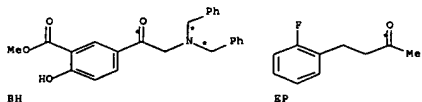
(87)



DB

RX(87) RCT EO 371-41-5, AY 78-95-5
PRO DB 81580-29-2
CAT 144-55-8 NaHCO₃

RX(88) OF 182 BH + EP ==> BL...

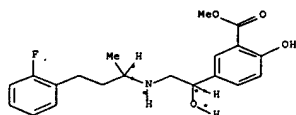


BH

EP

(88)

132

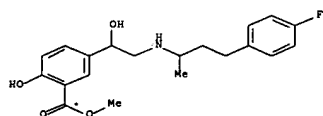


● HCl

BL
YIELD 76%

RX(88) RCT BH 36270-04-9, EP 63416-65-9
RGT H 7647-01-0 HCl
PRO BL 63416-66-0

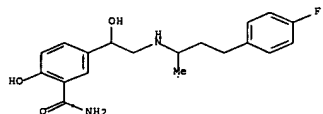
RX(89) OF 182 ...BI ==> EQ



● HCl

BI

(89)



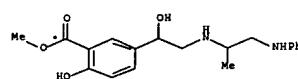
● HCl

EQ
YIELD 90%

133

RX(89) RCT BI 63416-60-4
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO EQ 64779-91-5

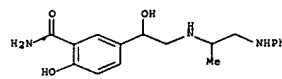
RX(90) OF 182 ...BV ==> BR



● 2 HCl

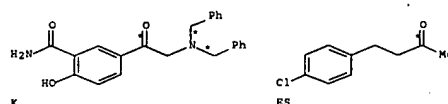
BV

(90)

BR
YIELD 30%

RX(90) RCT BV 81579-49-9
RGT AL 1336-21-6 NH4OH
PRO BR 81579-60-4

RX(91) OF 182 ...K + ES ==> ET



K

ES

(91)

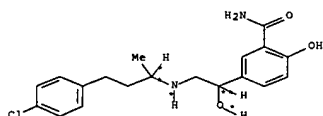
L27 ANSWER 8 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 95:61370 CASREACT Full-text
TITLE: Synthesis of substituted 3-amino alcohols by reduction
of oximes of β -keto alcohols
AUTHOR(S): Latypova, F. N.; Malina, Yu. F.; Unkovskii, B. V.
CORPORATE SOURCE: USSR
SOURCE: Khimiya i Tekhnologiya Organicheskikh Proizvodstv
(1979), 9(2), 3-8
CODEN: KTPOPN
DOCUMENT TYPE: Journal
LANGUAGE: Russian
CLASSIFICATION: 23-7 (Aliphatic Compounds)
Section cross-reference(s): 25

ABSTRACT:
Condensation reaction of HCHO with PhCOEt and MeOH containing KOH yielded 80% HOCH₂CHMeCOPh (I). Oximation of HOCRR1CHR2COR3 (R = R1 = R3 = Me, R2 = H; R = R1 = H, R2 = R3 = Me; R = H, R1 = R2 = R3 = Me) and I gave 65-85% yield of the corresponding HOCRR1CHR2CR3:NOH, which were reduced with Raney Ni and with LiAlH₄ to give 50-70% and 35-50% HOCRR1CHR2CHR3NH₂ (same R-R3), resp.

SUPPL. TERM: amino alc; oxime hydroxy ketone redn
INDEX TERM: Oximes
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(of β -hydroxy ketones, preparation and reduction of, β -amino alcs. by)
INDEX TERM: Ketones, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(oximation of)
INDEX TERM: Alcohols, preparation
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(amino, β -, preparation of, by reduction of oximes of β -hydroxy ketones)
INDEX TERM: 93-55-0
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation reaction of, with formaldehyde)
INDEX TERM: 50-00-0, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation reaction of, with propiophenone)
INDEX TERM: 123-42-2 565-79-7 3393-64-4
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(oximation of)
INDEX TERM: 16735-22-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and oximation of)
INDEX TERM: 17918-67-1P 69125-01-5P 78401-96-4P 78401-97-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of, β -amino alc. by)
INDEX TERM: 70772-78-0P 78401-94-2P 78401-95-3P 78420-43-6P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RX(1) OF 56 A * B ==> C...

134

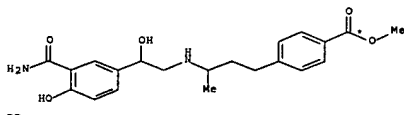


● HCl

ET
YIELD 13%

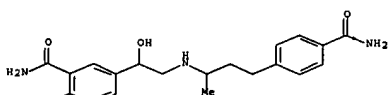
RX(91) RCT K 30566-92-8, ES 3506-75-0
RGT H 7647-01-0 HCl
PRO ET 64779-93-7

RX(92) OF 182 ...DR ==> EU



DR

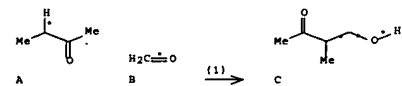
(92)



● HCl

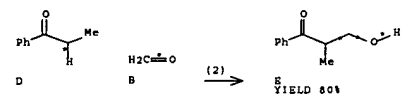
EU
YIELD 41%

RX(92) RCT DR 81580-11-2
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO EU 81580-12-3



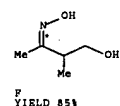
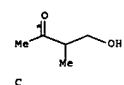
RX(1) RCT A 78-93-3, B 50-00-0
 PRO C 3393-64-4

RX(2) OF 66 D + B ==> E...



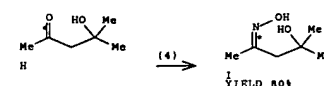
RX(2) RCT D 93-55-0, B 50-00-0
 PRO E 16735-22-1

RX(3) OF 66 ...C ==> F...



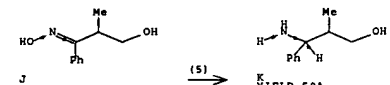
RX(3) RCT C 3393-64-4
 RGT G 7803-49-8 NH2OH
 PRO F 69125-01-5

RX(4) OF 66 H ==> I...



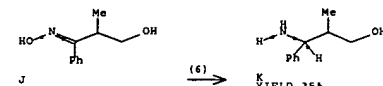
RX(4) RCT H 123-42-2
 RGT G 7803-49-8 NH2OH
 PRO I 17918-67-1

RX(5) OF 66 ...J ==> K



RX(5) RCT J 78401-97-5
 PRO K 78401-95-3

RX(6) OF 66 J ==> K

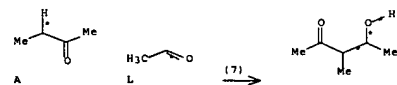


RX(6) RCT J 78401-97-5
 PRO K 78401-95-3

RX(7) OF 66 A + L ==> M...

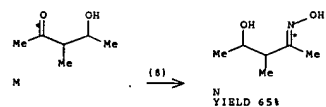
137

138



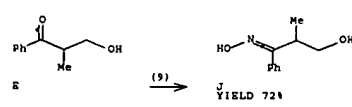
RX(7) RCT A 78-93-3, L 75-07-0
 PRO M 565-79-7

RX(8) OF 66 ...M ==> N...



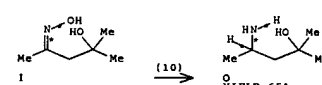
RX(8) RCT M 565-79-7
 RGT G 7803-49-8 NH2OH
 PRO N 78401-96-4

RX(9) OF 66 ...E ==> J...



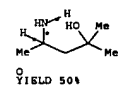
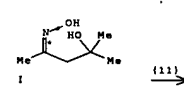
RX(9) RCT E 16735-22-1
 RGT G 7803-49-8 NH2OH
 PRO J 78401-97-5

RX(10) OF 66 ...I ==> O



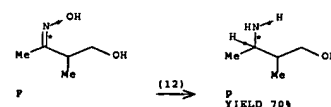
RX(10) RCT I 17918-67-1
 PRO O 70772-78-0

RX(11) OF 66 I ==> O



RX(11) RCT I 17918-67-1
 PRO O 70772-78-0

RX(12) OF 66 ...F ==> P

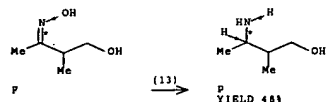


RX(12) RCT P 69125-01-5
 PRO P 78401-94-2

RX(13) OF 66 P ==> P

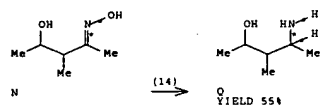
139

140



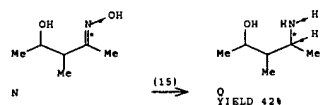
RX(13) RCT F 69125-01-5
PRO P 78401-94-2

RX(14) OF 66 ...N ==> Q



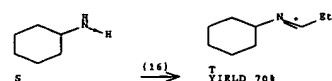
RX(14) RCT N 78401-96-4
PRO Q 78420-43-6

RX(15) OF 66 N ==> Q



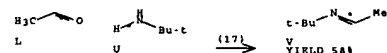
RX(15) RCT N 78401-96-4
PRO Q 78420-43-6

RX(16) OF 66 R + S ==> T...



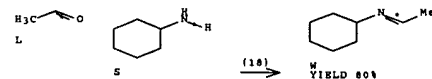
RX(16) RCT R 123-38-6, S 108-91-8
PRO T 1195-49-9

RX(17) OF 66 L + U ==> V...



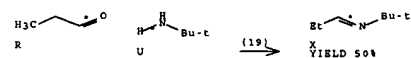
RX(17) RCT L 75-07-0, U 75-64-9
PRO V 7020-80-6

RX(18) OF 66 L + S ==> W...



RX(18) RCT L 75-07-0, S 108-91-8
PRO W 1193-93-7

RX(19) OF 66 R + U ==> X...

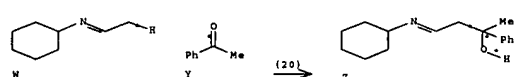


RX(19) RCT R 123-38-6, U 75-64-9
PRO X 7020-81-7

RX(20) OF 66 ...W + Y ==> Z...

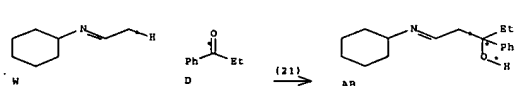
141

142



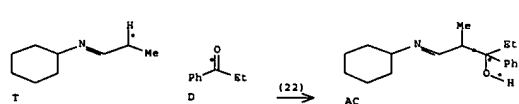
RX(20) RCT W 1193-93-7, Y 98-86-2
PRO Z 1217-04-5
CAT 816-43-3 LiNEt2

RX(21) OF 66 ...W + D ==> AB...



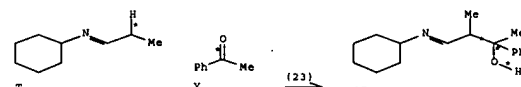
RX(21) RCT W 1193-93-7, D 93-55-0
PRO AB 343617-82-3
CAT 816-43-3 LiNEt2

RX(22) OF 66 ...T + D ==> AC...



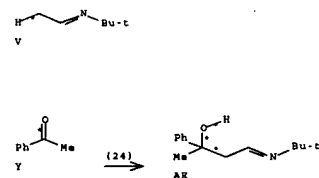
RX(22) RCT T 1195-49-9, D 93-55-0
PRO AC 343623-11-0
CAT 816-43-3 LiNEt2

RX(23) OF 66 ...T + Y ==> AD...



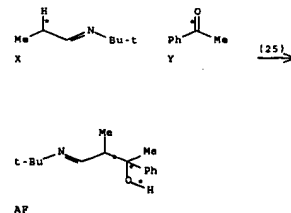
RX(23) RCT T 1195-49-9, Y 98-86-2
PRO AD 1712-88-5
CAT 816-43-3 LiNEt2

RX(24) OF 66 ...V + Y ==> AE...



RX(24) RCT V 7020-80-6, Y 98-86-2
PRO AE 343318-81-0
CAT 816-43-3 LiNEt2

RX(25) OF 66 ...X + Y ==> AF...

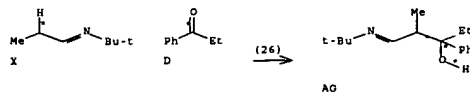


143

144

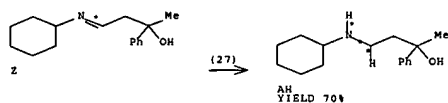
RX(25) RCT X 7020-81-7, Y 98-86-2
PRO AF 34323-16-0
CAT 816-43-3 LiNet2

RX(26) OF 66 ...X + D ==> AG...



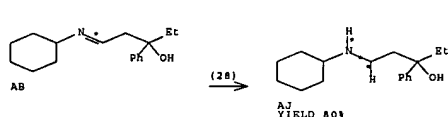
RX(26) RCT X 7020-81-7, D 93-55-0
PRO AG 343595-95-9
CAT 816-43-3 LiNet2

RX(27) OF 66 ...Z ==> AH



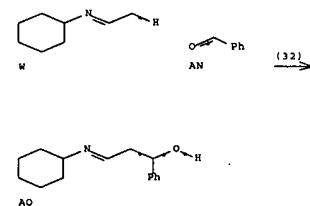
RX(27) RCT Z 1217-04-5
RGT AI 16853-85-3 LiAlH4
PRO AH 343596-78-1

RX(28) OF 66 ...AB ==> AJ



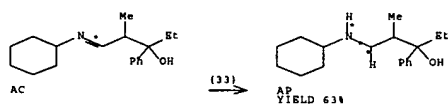
RX(28) RCT AB 343617-82-3
RGT AI 16853-85-3 LiAlH4
PRO AJ 75243-14-0

145



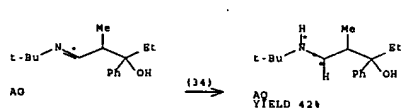
RX(32) RCT W 1193-93-7, AN 100-52-7
PRO AO 1215-49-2
CAT 816-43-3 LiNet2

RX(33) OF 66 ...AC ==> AP



RX(33) RCT AC 343623-11-0
RGT AI 16853-85-3 LiAlH4
PRO AP 343623-09-6

RX(34) OF 66 ...AG ==> AQ

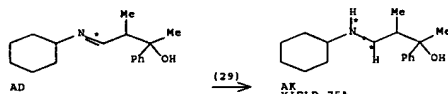


RX(34) RCT AG 343595-95-9
RGT AI 16853-85-3 LiAlH4
PRO AQ 343595-94-8

FILE 'HOME' ENTERED AT 15:33:48 ON 03 APR 2007

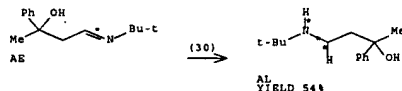
147

RX(29) OF 66 ...AD ==> AK



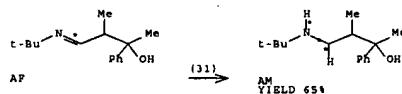
RX(29) RCT AD 1712-88-5
RGT AI 16853-85-3 LiAlH4
PRO AK 343617-70-9

RX(30) OF 66 ...AE ==> AL



RX(30) RCT AE 343310-81-0
RGT AI 16853-85-3 LiAlH4
PRO AL 75263-07-9

RX(31) OF 66 ...AF ==> AM



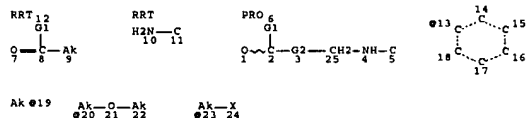
RX(31) RCT AF 343323-16-0
RGT AI 16853-85-3 LiAlH4
PRO AM 343323-15-9

RX(32) OF 66 ...W + AN ==> AO

146

SEARCH HISTORY

=> d stat que 127; d his nofile
L15 STR



VAR G1=19/20/23/13

RSP G2=(0-2) CH2

NODE ATTRIBUTES:

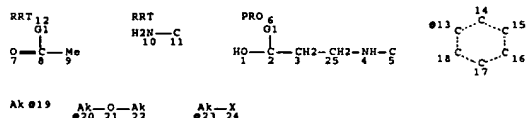
NSPEC IS RC AT 5
NSPEC IS RC AT 11
CONNECT IS E1 RC AT 1
CONNECT IS E1 RC AT 9
CONNECT IS E1 RC AT 19
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
OGCAT IS LOC SAT AT 9
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM ROL NOD SYM ROL
5 C PRO 11 C RRT
11 C RRT 5 C PRO
L19 150 SEA FILE=CASREACT SSS FUL L15 (722 REACTIONS)
L24 STR



VAR G1=19/20/23/13

NODE ATTRIBUTES:

NSPEC IS RC AT 5
NSPEC IS RC AT 11
CONNECT IS E1 RC AT 19
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 1

148

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM	ROL	NOD SYM	ROL
5 C	PRO	11 C	RRT
11 C	RRT	5 C	PRO

L27 8 SEA FILE=CASREACT SUB=L19 SSS FUL L24 (26 REACTIONS)

100.0% DONE 219 VERIFIED 26 HIT RXNS 8 DOCS
SEARCH TIME: 00.00.03

(FILE 'HOME' ENTERED AT 14:58:38 ON 03 APR 2007)

FILE 'CAPLUS' ENTERED AT 14:58:45 ON 03 APR 2007

E US2005-520362/APPS
L1 1 SEA ABB-ON US2005-520362/AP
D SCAN

FILE 'CASREACT' ENTERED AT 14:59:40 ON 03 APR 2007

E US2005-520362/APPS
L2 12 SEA ABB-ON MICHEL D7/AU
L3 72 SEA ABB-ON 3-AMINO ALCOHOL#
L4 2 SEA ABB-ON L2 AND L3
D SCAN
L5 STR
L6 1 SEA SSS SAM L5 (12 REACTIONS)
D SCAN

FILE 'STNGUIDE' ENTERED AT 15:06:32 ON 03 APR 2007

FILE 'CASREACT' ENTERED AT 15:08:11 ON 03 APR 2007

L7 SCREEN 1235
L8 1 SEA SSS SAM L5 AND L7 (12 REACTIONS)

FILE 'STNGUIDE' ENTERED AT 15:09:47 ON 03 APR 2007

FILE 'CASREACT' ENTERED AT 15:11:33 ON 03 APR 2007

L9 STR L5
L10 1 SEA SSS SAM L9 AND L7 (12 REACTIONS)
L11 STR L9
L12 3 SEA SSS SAM L11 AND L7 (7 REACTIONS)
D SCAN
D QUS
L13 STR L11
L14 3 SEA SSS SAM L13 (7 REACTIONS)
L15 STR L13
L16 4 SEA SSS SAM L15 (33 REACTIONS)
L17 3 SEA ABB-ON L16 NOT (L12 OR L14)
D SCAN
D QUS L15

L18 27925 SEA SSS FUL L15 (367857 REACTIONS) EXTEND
L19 150 SEA SSS FUL L15 (722 REACTIONS)
SAVE TEMP L19 YOU362CASRE/A
L20 STR L15
L21 3 SEA SUB=L19 SSS SAM L20 (7 REACTIONS)
D SCAN
D STAT QUS L19
L22 STR L15
L23 8 SEA SUB=L19 SSS SAM L22 (31 REACTIONS)
D STAT QUS L21
L24 STR L20
L25 1 SEA SUB=L19 SSS SAM L24 (1 REACTIONS)
D SCAN
L26 66 SEA SUB=L19 SSS FUL L24 (219 REACTIONS) EXTEND
L27 8 SEA SUB=L19 SSS FUL L24 (26 REACTIONS)
SAVE TEMP L27 YOU362SUB1/A
L28 0 SEA ABB-ON L27 AND L4

FILE 'CASREACT' ENTERED AT 15:29:11 ON 03 APR 2007

D QUS L4
D IALL L4 1
D IALL L4 2
D STAT QUS L27
D IALL L27 1-8

FILE 'HOME' ENTERED AT 15:33:48 ON 03 APR 2007

D STAT QUS L27

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